REMARKS

The claims have been amended to further clarify the meaning of the term "associated values" so that the claim limitations relate more clearly to practical applications for analysis of data acquired from biological samples. As amended, the claims now clearly state that the associated values are acquired by a process where biological samples containing a plurality of genes are hybridized to one or more microarrays of probes, thus measuring the levels of mRNA or protein in the biological samples. This is how the associated values are acquired.

35 U.S.C. 101 REJECTION

Claims 1-22, 28-30, 33, 44, 46, 58 and 60 remain rejected under 35 U.S.C. 101. New Claims 65 and 66 are rejected as well as directed to non-statutory subject matter. The rejection is respectfully traversed.

The Examiner is of the opinion that the claimed invention of the rejected claims does not produce a useful, concrete and tangible result, but rather merely encompass combinations of groups of data about statistical differences in mRNA or protein levels, with no specific output that meets the concrete, tangible and useful criteria, or merely describes "functional descriptive material." We disagree insofar as the rejection is applied to the claims as amended. We believe that one skilled in the art will think that the claimed invention of the Claims as amended produces a useful, concrete and tangible result.

As clearly explained in the present Application, one of the major problems in analysis of gene related data is that the process normally used in collecting information to find statistically significant biological phenomena in biological samples is by its very nature noisy. Thus, it is difficult to distinguish between measured variations in mRNA or protein levels due to the noise inherent in the process from variations in mRNA or protein levels caused by statistically significant biological phenomena. This is overcome in the claims as amended by deriving or providing an expected value of the parameter, where the expected value is indicative of extent of variations in the parameter introduced by the data collection process itself. Only when the observed phenomenon results in values of the parameter that are significant compared to such expected value will the gene exhibiting such characteristics be identified to be associated with statistically significant biological phenomena. This results in a better success rate of detecting *bona fide* changes in gene expression and a reduced false discovery rate in the examples

described in the present application. This limitation is present in all of the rejected Independent Claims. An embodiment of this feature is described in more detail on pages 12 –14 of the specification, and the improved results over conventional techniques on pages 15-18.

The above feature is taken one step further in claims 28, 46, 60 and 66. This is illustrated in the embodiment described on pages 12-14 of the present application. The sets of values of the relative difference d(i) in expression of the genes are permuted to arrive at sets of relative difference values different from the original sets. The values in the new sets are then ranked, and an expected value of such relative difference for each rank is provided. Thus, comparing the largest relative difference among all the genes to the largest relative differences from the permutations provides one possible test for identifying genes to be of statistical significance. Therefore, the average of the largest relative differences from the permutations is the expected relative difference for such gene. A comparison of the relative difference of such gene with its expected value can be used as control as to whether statistical significance should be assigned to such gene. The same reasoning applies to the gene of the second highest relative difference and comparison to the second largest relative differences from the permutations, and so on for all the genes involved in the calculation. This process involving ranking the relative difference values further enhances the ability to identify biological phenomenon from noise inherent in the data collection and analysis.

Another difficulty in making use of microarray data is due to the fact that the expression levels of the genes have a wide range of values or scattered values. Another limitation present in some of the Claims amended solves this problem by adjusting the parameters of the plurality of genes so that variables related to the parameters are substantially independent or variations of scattered values or average associated values of the genes over the sets. The scattered values are defined by standard deviation of the associated values in the sets. In the embodiment described on pages 11 and 12 of the present specification, this is performed by adjusting the value of S_0 in equation 1 on page 10 so that the parameter d(i) is substantially independent of the wide variations and scattered values or average associated values of the genes, so that all of the microarray data can be effectively used.

The above-described limitations in the Claims as amended are clearly described in the paper entitled "*Significance analysis of microarrays applied to the ionizing radiation response*," Virginia Goss Tusher, et al., Proceedings of the National Academy of Sciences of the United

States of America (PNAS), (published on line before print, April 17, 2001, 10.1073/pnas. 091062498), PNAS, April 24, 2001, Volume 98, No. 9, pages 5116-5121. As will be noted, the content of this article is essentially captured in the present Application, and the inventors of this application are its authors. As referred to in the present Application and in this article, the various techniques described in the article are referred to as "SAM," and this article is referred to herein as the "SAM article."

A copy of the SAM article is attached, along with a printout of the references that cite or quote this article. Thus, there are roughly around 500 published articles that refer to the SAM paper by the inventors as of September of 2005. This makes the article one of the most cited or referred to published articles in its field of expertise. Enclosed are two of the articles that refer to the SAM article.

Attached is the article entitled "An expression signature for p53 status in human breast cancer predicts mutation status, transcriptional effects, and patient survival," by Lance Miller et al., (published on line before print September 2, 2005, 10.1073/pnas. 0506230102), PNAS, September 20, 2005, Volume 102, No. 38, pages 13550-13555. As stated on page 6 of this article: "Univariate analysis by statistical analysis of microarrays (SAM) (22) identified 6,545 Affymetrix probe sets representing ≈ 5,290 distinct genes whose expression patterns distinguished P53 mt and wt tumors with a false discovery rate (q value) < 1% and d score (modified t statistic) > 2.0 ..., further illuminating the extensive nature of the molecular variation underlying p53 status." Reference to "(SAM)(22)" in the quote refers to the above SAM article.

SAM software that implements the features described in the present application and the SAM article has been widely licensed since 2001. Attached is a Bulletin of information available on the internet on licensing such software.

Attached is a declaration by Dr. Gilbert Chu, one of the inventors of the present application, stating that the SAM software that has been licensed to the public implements the two claim limitations in the claims as amended discussed above. Dr. Chu further states in his declaration that he believes that the analysis using SAM in the above quote from the Miller article employs the two claim limitations discussed above through the use of SAM software.

Thus, as can be seen from the above quote, the authors of the Miller, et al. article use features of the two claim limitations in the claims as amended to identify about 5290 distinct

genes whose expression patterns distinguished the p53 gene tumors. In other words, by making use of the above-described two claim limitations of the Claims as amended, without more, the authors of the Miller, et al. article identified around 5290 distinct genes whose associated values differ by an amount of statistical significance among the data, for distinguishing the p53 gene tumors. As described in this article by Miller, et al., certain correlations that are useful for analyzing human breast cancer for predicting mutation status transcriptional effects and patient survival are then developed. Thus, this article is direct evidence that to one of ordinary skill in the art, the two limitations in the Claims as amended produce a useful, concrete and tangible result. This contradicts the Examiner's positions if the rejection is applied to the claims as amended.

Another article citing or referring to the SAM article is "Ancestral antibiotic resistance in Mycobacterium tuberculosis," by Rowan P. Morris, et al., (published on line before print August 15, 2005, 10.1073/pans. 0505446102), PNAS, August 23, 2005, Volume 102, No. 34, pages 12200-12205. As described on page 5 of this article by Morris et al., monocytes were infected by mycobacterium and activated. Labeling of RNA and hybridizations were performed. Then, "data from each experimental condition was analyzed separately by using significance analysis of microarrays (22) with a false discovery ration $\leq 0.3\%$." The reference to "significance analysis of microarrays (22)" is to the SAM article. Dr. Chu's declaration states that he believes that the data analysis using SAM in the above quote from the Morris article uses the two claim limitations discussed above through the use of SAM software.

Thus, in each of the articles by Miller et al. and Morris et al., the two claim limitations in the claims as amended discussed above, apparently without more, allow genes whose associated values differ by an amount of statistical significance to be identified for very practical, tangible, useful and concrete applications, so that the invention in the claims as amended are recognized by those skilled in the art to produce a useful, concrete and tangible result.

The above two articles are merely two of the around 500 articles that refer to or use the techniques in the SAM article. More examples of useful, concrete and tangible results produced by application of the invention in the Claims as amended can undoubtedly be found in other articles in addition to the two described above. We therefore believe that there is ample evidence that the invention of the Claims as amended produces a useful, concrete and tangible result,

contrary to the opinion of the Examiner. If the Examiner disagrees, it is respectfully requested that the Examiner explain in detail the reasons why such rejection is still maintained in the face of overwhelming evidence that weighs against such position.

In responding to the Applicant's arguments, the Office Action stated that "in the instant Claims, the Claims as a whole, do not result in the physical transformation and as a whole do not constitute a practical application of an abstract idea" quoting *State Street Bank & Trust v. Signature Financial Group,* 47 USPQ 2d at 1600. The Office Action continues: "Thus, data transformation is not necessarily a physical transformation, as it is the result as a whole that is the focus. It is noted that the *Arrhythmia* case, for example, 'constituted a practical Application of an abstract idea because it corresponded to a useful, concrete, intangible thing – the condition of the patient's heart, which is not the case in the instant claimed invention."

We disagree with the above statement by the Examiner. The various claim elements in the rejected claims do not merely manipulate abstract concepts or data, but the associated values that are manipulated correspond to useful, concrete and tangible things – the levels of mRNA or levels of protein. As further clarified by the claim amendments herein, these levels are measured from biological samples containing the genes. These levels, may in turn, indicate certain significant biological characteristics or activity. As clearly described in the specification, such biological characteristics or activity may, for example, be caused by the effect of radiation on genes, by inducing or repressing the genes. The Examiner may again object on the grounds that there is inadequate nexus between such practical real world applications and the different claim elements in the rejected Claims. We believe, however, that there is no requirement under 35 U.S.C. § 101 that very specific applications such as gene inducement or repression need to be recited in the claims themselves. This is true in the *Arrhythmia* case as well. As will be noted from the *Arrhythmia* case, the condition of the patient's heart is also not directly recited in the Claims at issue. The Claim at issue in the *Arrhythmia* case merely recites the steps of converting QRS signals to time segments, applying a portion of the time segments in reverse time order to high pass filter means, determining an arithmetic value of the amplitude of the output of the filter and comparing the value with a pre-determined level. The patient's heart condition does not appear anywhere in the claim language. The different data that is manipulated by the method in *Arrhythmia* are an indication of the condition of the patient's heart, even though the condition of the patient's heart is not directly recited in the Claim. Analogous to the Claim in *Arrhythmia*, the

associated values that are manipulated in the Claims as amended indicate significant biological characteristics or activity. When the biological samples analyzed are samples that have been irradiated and control samples that have not irradiated, the invention of the claims as amended will reveal the genes that have been suppressed and those that have been induced. Analogous applications are also shown in the Miller and Morris articles. The claims as amended are no different from the *Arrhythmia* claims where the signals manipulated in the claimed method represent heart activity of a patient without actually reciting in the claim the condition of the patient's heart.

We therefore disagree with the Examiner's opinion quoted above.

UTILITY

Claims 1-22, 28-30, 33, 44, 46, 58, 60, 65 and 66 remain rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The rejection is respectfully traversed. The discussion above clearly describes many utilities of the invention in the rejected claims. Withdrawal of this rejection is respectfully requested.

In the amendment mailed January 19, 2005, Applicants set forth a number of specific Utilities on page 12 of the Amendment. These include the identification of genes whose DNA has been damaged by exposure to radiation, the identification of genes in tumors (page 18, line 24) or the identification of genes whose expression correlates with the survival time of patients (page 19, line 16), or with tumor stage (sentence bridging pages 19 and 20). These Utilities were rejected by the Examiner in the Office Action mailed April 19, 2005 on the ground that the Claims do not recite steps that are applicable to any of these uses and that there is no adequate nexus between the disclosed subject matter and these asserted Utilities. We disagree.

As will be evident from the present Application, as well as the articles described above, the utility of the invention of the rejected Claims is achieved by simply applying the steps involved to particular biological samples. In the present Application, the recited features were applied to samples that were grown with exposure to radiation and samples that were grown without exposure to radiation. The invention of the claims as amended then enables the identification of genes whose expression has been induced or repressed by radiation. The same is true in the case of the above articles involving tumor and breast cancer analysis. This is true

also in the case of the Claims in *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 22 U.S.P.Q. 2d, 1033 at 1038. Claim 1 in the *Arrhythmia* case recites steps that merely manipulate QRS signals which represent signals obtained from the heart, but otherwise do not recite anything involving the patient's heart condition. The Court nevertheless deems such claim to have utility under 35 U.S.C. 101. In the same manner, it is believed that the Claims as amended have utility, without having to recite specific applications, which would unduely limit the claims.

By rejecting the Claims based on the inadequate nexus between the disclosed subject matter and the asserted utilities, the Examiner is in fact requiring Applicants to restrict the Claims to particular applications. This is against the rule articulated by the Court of Appeals for the Federal Circuit in *State Street Bank & Trust v. Signature Financial Group,* 47 USPQ 2d 1600 at 1604. In the ruling by the lower court in this case, the patent was found invalid "because the '056 patent is claimed [sic] sufficiently broadly to foreclose any computer-implemented accounting method necessary to manage this type of financial structure." In response, the Court of Appeals for the Federal Circuit stated as follows: "whether the patent's Claims are too broad to be patentable is not to be judged under Section 101, but rather under Sections 102, 103, and 112. Assuming the above statement to be correct, it has nothing to do with what is claimed is statutory subject matter."

Rejection under 35 U.S.C. 112 First Paragraph

Claims 1-22, 28-30, 33, 44, 46, 58, 60 and new Claims 65 and 66 are rejected under 35 U.S.C. 112 first paragraph for failing to comply with the written description requirement. Specifically, Claims 1, 28, 46, 58 and 60, 64 and 65 are rejected on the ground that it still includes the terms "protein." We disagree. As expressly stated in lines 1-5 on page 4 of the specification, one of the examples given for of the values associated with genes are the levels of protein encoded by the genes. This is also explicitly claimed in Claim 4 of the Claims as originally filed. As noted in MPEP 2163, page 2100-173, there is a strong presumption that an adequate written description of the claimed invention is present when the Application is filed. Further, the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. The Examiner has failed to present any evidence why persons skilled in the art would not recognize a description of the invention originally present both in the Claims and the Summary

of the Invention and that the claims still fail to comply with 35 U.S.C. 112 for lacking an adequate written description. It is respectfully requested that this rejection be withdrawn.

CONCLUSION

In view of the amendments and remarks contained herein, it is believed that all claims are in condition for allowance and an indication of their allowance is requested. However, if the Examiner is aware of any additional matters that should be discussed, a call to the undersigned attorney at: (415) 318-1162 would be appreciated.

Respectfully submitted,

July 20, 2006

James S. Hsue Date
Reg. No. 29,545

PARSONS HSUE & de RUNTZ LLP
595 Market Street, Suite 1900
San Francisco, California 94105
Telephone: 415.318.1160 (main)
Telephone. 415.318.1162 (direct)
Fax: 415.693.0194

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Statistics / Genetics

Significance analysis of microarrays applied to the ionizing radiation response

Virginia Goss Tusher[*], Robert Tibshirani[†], and Gilbert Chu[*,‡]

[*] Departments of Medicine and Biochemistry, Stanford University, 269 Campus Drive, Center for Clinical Sciences Research 1115, Stanford, CA 94305-5151; and [†] Department of Health Research and Policy and Department of Statistics, Stanford University, Stanford, CA 94305

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Abstract

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Microarrays can measure the expression of thousands of genes to identify changes in expression between different biological states. Methods are needed to determine the significance of these changes while accounting for the enormous number of genes. We describe a method, Significance Analysis of Microarrays (SAM), that assigns a score to each gene on the basis of change in gene expression relative to the standard deviation of repeated measurements. For genes with scores greater than an adjustable threshold, SAM uses permutations of the repeated measurements to estimate the percentage of genes identified by chance, the false discovery rate (FDR). When the transcriptional response of human cells to ionizing radiation was measured by microarrays, SAM identified 34 genes that changed at least 1.5-fold with an estimated FDR of 12%, compared with FDRs of 60 and 84% by using conventional methods of analysis. Of the 34 genes, 19 were involved in cell cycle regulation and 3 in apoptosis. Surprisingly, four nucleotide excision repair genes were induced, suggesting that this repair pathway for UV-damaged DNA might play a previously unrecognized role in repairing DNA damaged by ionizing radiation.

Introduction

DNA microarrays contain oligonucleotide or cDNA probes for measuring the expression of thousands of genes in a single hybridization experiment. Although massive amounts of data are generated, methods are needed to determine whether changes in gene expression are experimentally significant. Cluster analysis of microarray data can find coherent patterns of gene expression (1) but provides little information about statistical significance. Methods based on conventional *t* tests provide the probability (*P*) that a difference in gene expression occurred by chance (2, 3). Although

$P = 0.01$ is significant in the context of experiments designed to evaluate small numbers of genes, a microarray experiment for 10,000 genes would identify 100 genes by chance. This problem led us to develop a statistical method adapted specifically for microarrays, Significance Analysis of Microarrays (SAM).

SAM identifies genes with statistically significant changes in expression by assimilating a set of gene-specific *t* tests. Each gene is assigned a score on the basis of its change in gene expression relative to the standard deviation of repeated measurements for that gene. Genes with scores greater than a threshold are deemed potentially significant. The percentage of such genes identified by chance is the false discovery rate (FDR). To estimate the FDR, nonsense genes are identified by analyzing permutations of the measurements. The threshold can be adjusted to identify smaller or larger sets of genes, and FDRs are calculated for each set. To demonstrate its utility, SAM was used to analyze a biologically important problem: the transcriptional response of lymphoblastoid cells to ionizing radiation (IR).

Materials and Methods

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Preparation of RNA. Human lymphoblastoid cell lines GM14660 and GM08925 (Coriell Cell Repositories, Camden, NJ) were seeded at 2.5×10^5 cells/ml and exposed to IR 24 h later. RNA was isolated, labeled, and hybridized to the HUGENEFL GENECHIP microarray according to manufacturer's protocols (Affymetrix, Santa Clara, CA).

Microarray Hybridization. Each gene in the microarray was represented by 20 oligonucleotide pairs, each pair consisting of an oligonucleotide perfectly matched to the cDNA sequence, and a second oligonucleotide containing a single base mismatch. Because gene expression was computed from differences in hybridization to the matched and mismatched probes, expression levels were sometimes reported by

the GENECHIP ANALYSIS SUITE software as negative numbers.

Northern Blot Hybridization. Total RNA (15 μg) was resolved by agarose gel electrophoresis, transferred to a nylon membrane, and hybridized to specific radiolabeled DNA probes, which were prepared by PCR amplification.

Results

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RNA was harvested from wild-type human lymphoblastoid cell lines, designated 1 and 2, growing in an unirradiated state (U) or in an irradiated state (I) 4 h after exposure to a modest dose of 5 Gy of IR. RNA samples were labeled and divided into two identical aliquots for independent hybridizations, A and B. Thus, data for 6,800 genes on the microarray were generated from eight hybridizations (U1A, U1B, U2A, U2B, I1A, I1B, I2A, and I2B).

We scaled the data from different hybridizations as follows. A reference data set was generated by averaging the expression of each gene over all eight hybridizations. The data for each hybridization were compared with the reference data set in a cube root scatter plot. We chose the cube root scatter plot because it resolved the vast majority of genes that are expressed at low levels and permitted the inclusion of negative levels of expression that are sometimes generated by the GENECHIP software. A linear least-squares fit to the cube root scatter plot was then used to calibrate each hybridization.

After scaling, a linear scatter plot was generated for average gene expression in the four A aliquots (U1A, I1A, U2A, and U2A) vs. the average in the four B aliquots (U1B, I1B, U2B, and U2B), a partitioning of the data that eliminates biological changes in gene expression (Fig. 1*A*). The linear scatter plot confirmed that the data were generally reproducible but failed to resolve genes expressed at low levels. Better resolution of these genes was achieved by the cube root scatter plot (Fig. 1*B*), which

revealed three salient features: the large percentage of genes (24%) assigned negative levels of expression, the large percentage of genes with low levels of expression, and the low signal-to-noise ratio at low levels of expression.

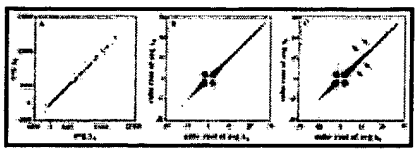

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Fig. 1. Gene expression measured by microarrays. (*A*) Linear scatter plot of gene expression. Each gene (*i*) in the microarray is represented by a point with coordinates consisting of average gene expression measured from the four A hybridizations (avg x_A) and the average gene expression in the four B hybridizations (avg x_B). (*B*) Cube root scatter plot of gene expression. The average gene expression from the A and B hybridizations have been plotted on a cube root scale to resolve genes expressed at low levels. (C) Cube root scatter plot of average gene expression from the four hybridizations with uninduced cells (avg x_U) and induced cells 4 h after exposure to 5 Gy of IR (avg x_I). Some of the genes that responded to IR are indicated by arrows.

To assess the biological effect of IR, a scatter plot was generated for average gene expression in the four irradiated states vs. the four unirradiated states (compare Fig. 1 *B* and *C*). A few of the potentially significant changes in gene expression are indicated by arrows in Fig. 1*C*, but the effect was not easily quantified, and a method was needed to identify changes with statistical confidence.

Our approach was based on analysis of random fluctuations in the data. In general, the signal-to-noise ratio decreased with decreasing gene expression (Fig. 1). However, even for a given level of expression, we found that fluctuations were gene specific. To account for gene-specific fluctuations, we defined a statistic based on the ratio of change in gene expression to standard deviation in the data for that gene. The

"relative difference" $d(i)$ in gene expression is:

$$d(i) = \frac{\bar{x}_I(i) - \bar{x}_U(i)}{s(i) + s_0} \quad [1]$$

where $\bar{x}_I(i)$ and $\bar{x}_U(i)$ are defined as the average levels of expression for gene (i) in states I and U, respectively. The "gene-specific scatter" $s(i)$ is the standard deviation of repeated expression measurements:

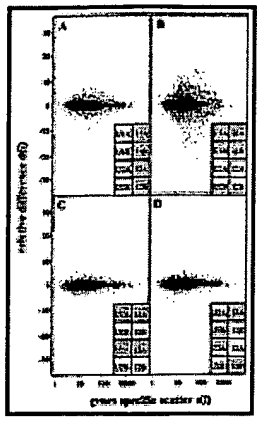
$$s(i) = \sqrt{a\left\{\sum_m [x_m(i) - \bar{x}_I(i)]^2 + \sum_n [x_n(i) - \bar{x}_U(i)]^2\right\}} \quad [2]$$

where Σ_m and Σ_n are summations of the expression measurements in states I and U, respectively, $a = (1/n_1 + 1/n_2)/(n_1 + n_2 - 2)$, and n_1 and n_2 are the numbers of measurements in states I and U (four in this experiment).

To compare values of $d(i)$ across all genes, the distribution of $d(i)$ should be independent of the level of gene expression. At low expression levels, variance in $d(i)$ can be high because of small values of $s(i)$. To ensure that the variance of $d(i)$ is independent of gene expression, we added a small positive constant s_0 to the denominator of Eq. 1. The coefficient of variation of $d(i)$ was computed as a function of $s(i)$ in moving windows across the data. The value for s_0 was chosen to minimize the coefficient of variation. For the data in this paper, this computation yielded $s_0 = 3.3$.

Scatter plots of $d(i)$ vs. $s(i)$ are shown in Fig. 2. The scatter plot for relative difference between states I and U is shown in Fig. 2*A*. By contrast, the scatter plot for relative difference between cell lines 1 and 2 shows more marked changes in Fig. 2*B*. These relative differences exceeded random fluctuations in the data, as measured by the relative difference between hybridizations A and B in Fig. 2*C*.

Fig. 2. Scatter plots of relative difference in gene



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expression $d(i)$ vs. gene-specific scatter $s(i)$. The data were partitioned to calculate $d(i)$, as indicated by the bar codes. The shaded and unshaded entries were used for the first and second terms in the numerator of $d(i)$ in Eq. 1. (*A*) Relative difference between irradiated and unirradiated states. The statistic $d(i)$ was computed from expression measurements partitioned between irradiated and unirradiated cells. (*B*) Relative difference between cell lines 1 and 2. The statistic $d(i)$ was computed from expression measurements partitioned between cell lines 1 and 2. (*C*) Relative difference between hybridizations A and B. The statistic $d(i)$ was computed from the permutation in which the expression measurements were partitioned between the equivalent hybridizations A and B. (*D*) Relative difference for a permutation of the data that was balanced between cell lines 1 and 2.

Although the relative difference computed from hybridizations A and B provided a control for random fluctuations, additional controls were needed to assign statistical significance to the biological effect of IR. Instead of performing more experiments, which are expensive and labor intensive, we generated a large number of controls by computing relative differences from permutations of the hybridizations for the four irradiated and four unirradiated states. To minimize potentially confounding effects from differences between the two cell lines, we analyzed the data by using the 36 permutations that were balanced for cell lines 1 and 2. Permutations were defined as balanced when each group of four experiments contained two experiments from cell line 1 and two experiments from cell line 2. Fig. 2 *C* and *D* are examples of balanced permutations.

To find significant changes in gene expression, genes were ranked by magnitude of their $d(i)$ values, so that $d(1)$ was the largest relative difference, $d(2)$ was the second largest relative difference, and $d(i)$ was the ith largest relative difference. For each of the 36 balanced permutations, relative differences $d_p(i)$ were also calculated, and the

genes were again ranked such that $d_p(i)$ was the ith largest relative difference for permutation p. The expected relative difference, $d_E(i)$, was defined as the average over the 36 balanced permutations, $d_E(i) = \Sigma_p d_p(i)/36$.

To identify potentially significant changes in expression, we used a scatter plot of the observed relative difference $d(i)$ vs. the expected relative difference $d_E(i)$ (Fig. 3*A*). For the vast majority of genes, $d(i) \cong d_E(i)$, but some genes are represented by points displaced from the $d(i) = d_E(i)$ line by a distance greater than a threshold Δ. For example, the threshold $\Delta = 1.2$ illustrated by the broken lines in Fig. 3*A* yielded 46 genes that were "called significant." These 46 genes are shown in the context of the scatter plot for $d(i)$ vs. $s(i)$ (Fig. 3*B*) and in the scatter plot for the cube root of gene expression $\bar{x}_I(i)$ vs. $\bar{x}_U(i)$ (Fig. 3*C*). Genes identified by $d(i)$ do not necessarily have the largest changes in gene expression.

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Fig. 3. Identification of genes with significant changes in expression. (*A*) Scatter plot of the observed relative difference $d(i)$ versus the expected relative difference $d_E(i)$. The solid line indicates the line for $d(i) = d_E(i)$, where the observed relative difference is identical to the expected relative difference. The dotted lines are drawn at a distance $\Delta = 1.2$ from the solid line. (*B*) Scatter plot of $d(i)$ vs. $s(i)$. (*C*) Cube root scatter plot of average gene expression in induced and uninduced cells. The cutoffs for 2-fold induction and repression are indicated by the dashed lines. In *A-C*, the 46 potentially significant genes for $\Delta = 1.2$ are indicated by the squares.

To determine the number of falsely significant genes generated by SAM, horizontal

cutoffs were defined as the smallest $d(i)$ among the genes called significantly induced and the least negative $d(i)$ among the genes called significantly repressed. The number of falsely significant genes corresponding to each permutation was computed by counting the number of genes that exceeded the horizontal cutoffs for induced and repressed genes. The estimated number of falsely significant genes was the average of the number of genes called significant from all 36 permutations. For $\Delta = 1.2$, the permuted data sets generated an average of 8.4 falsely significant genes, compared with 46 genes called significant, yielding an estimated FDR of 18% (Table 1). As Δ decreased, the number of genes called significant by SAM increased but at the cost of an increasing FDR. (Omitting s_0 from Eq. 1 produced higher FDRs of 45, 35, and 28% for $\Delta = 0.6$, 0.9, and 1.2.)

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Table 1. Comparison of methods for identifying changes in gene expression

Our method for setting thresholds provides asymmetric cutoffs for induced and repressed genes. The alternative is the standard t test, which imposes a symmetric horizontal cutoff, with $d(i) > c$ for induced genes and $d(i) < -c$ for repressed genes. However, the asymmetric cutoff is preferred because it allows for the possibility that $d(i)$ for induced and repressed genes may behave differently in some biological experiments.

SAM proved to be superior to conventional methods for analyzing microarrays (Table 1 and Fig. 4*A*). First, SAM was compared with the approach of identifying genes as significantly changed if an R-fold change was observed. In this "fold change" method, $r(i) = \bar{x}_I(i)/\bar{x}_U(i)$, and gene (i) was called significantly changed if $r(i) > R$ or $r(i) < 1/R$.

To permit computation of $r(i)$ from negative values for gene expression, $\bar{x}_I(i)$ and $\bar{x}_U(i)$

were converted to 10 when their values were negative or less than 10. The results of this procedure yielded unacceptably high FDRs of 73-84%.

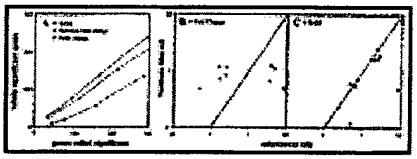

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Fig. 4. Comparison of SAM to conventional methods for analyzing microarrays. (*A*) Falsely significant genes plotted against number of genes called significant. Of the 57 genes most highly ranked by the fold change method, 5 were included among the 46 genes most highly ranked by SAM. Of the 38 genes most highly ranked by the pairwise fold change method, 11 were included among the 46 genes most highly ranked by SAM. These results were consistent with the FDR of SAM compared to the FDRs of the fold change and pairwise fold change methods. (*B*) Northern blot validation for genes identified by the fold change method. Values of $r(i)$ are plotted for genes chosen at random from the 57 genes most highly ranked by the fold change method. (*C*) Validation for genes identified by SAM. Results are plotted for genes chosen at random from the 46 genes most highly ranked by SAM. Genes analyzed by Northern blot are represented by circles. TNF-α was validated by using a PreDeveloped TaqMan assay (PE Biosystems) and is represented by a square. The straight lines in *B* and *C* indicate the position of exact agreement between Northern blot and microarray results.

Another approach attempts to account for uncertainty in the data by identifying genes as significantly changed if an *R*-fold change is observed consistently between paired samples (4). To apply this "pairwise fold change" method to our four data sets before IR and four data sets after IR, changes in gene expression were declared significant if 12 of 16 pairings satisfied the criteria $r(i) > R$ or $r(i) < 1/R$. Despite the demand for consistent changes between paired samples, this method yielded FDRs of 60-71%.

To understand why fold-change methods fail, note that the vast majority of genes are expressed at low levels where the signal-to-noise ratio is very low (Fig. 3*C*). Thus, 2-fold changes in gene expression occur at random for a large number of genes. Conversely, for higher levels of expression, smaller changes in gene expression may be real, but these changes are rejected by fold-change methods. The pairwise fold-change method provides modest improvement but remains inferior to SAM.

Of the 46 genes most highly ranked by SAM (Δ = 1.2), 36 increased or decreased at least 1.5-fold (R = 1.5). The number of falsely significant genes that met these two criteria was 4.5, corresponding to a FDR of 12% (Table 1). Fas was identified three times as alternately spliced forms, leaving 34 independent genes (Table 2). As an indication of biological validity, 10 of the 34 genes have been reported in the literature as part of the transcriptional response to IR. TNF-$_\alpha$ was reported to be induced by other investigators (5) but was repressed here. Quantitative reverse transcription-PCR confirmed this result.

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Table 2. Genes with changes in expression called significant by SAM

To test the validity of SAM directly, we performed Northern blots for genes that were randomly selected from the 46 and 57 genes most highly ranked by SAM ($_\Delta$ = 1.2) and the fold-change method (at least 3.6-fold change), respectively. Northern blots showed little correlation with the genes identified by the fold change method (Fig. 4*B*), but strong correlation with the genes identified by SAM (Fig. 4*C*). Indeed, Northern blots contradicted only 1 (maxiK) of 11 genes identified by SAM, consistent with our estimated FDR.

Nineteen of the 34 genes most highly ranked by SAM appear to be involved in the cell

cycle. Three are known to be induced in a p53-dependent manner: p21, cyclin G1, and mdm2 (6-8). Six cell cycle genes were repressed: E2-EPF, p55cdc, cyclin B, ckshs2, cdc25, and wee1 (9, 10). Five genes encoding the mitotic machinery were also repressed: PLK-1, MKLP-1, MCAK, C-TAK1, CENP-E (11-13). Three genes involved in cell proliferation were induced or repressed: PTP(CAAX1), LPAP, and c-myc (14-18). Some responses appeared paradoxical. For example, cdc25 phosphatase and wee1 kinase have antagonistic effects on the phosphorylation state of cdc2, but both genes were repressed. Repression of these genes together with the mitotic genes may represent a damage response that dismantles the cell cycle machinery until the cell has repaired the damaged DNA.

Four of the 34 genes play roles in DNA repair, but none are involved in the repair of IR-induced double-strand breaks. Instead, the genes (p48, XPC, gadd45, PCNA) have roles in nucleotide excision repair, a pathway conventionally associated with UV-induced damage (19-22). We confirmed the induction of these genes by Northern blot (23-25). Fornace *et al.* reported defective removal of base damage induced by IR in xeroderma pigmentosum cells (26). Leadon *et al.* reported that a novel DNA repair pathway involving long excision repair patches of at least 150 nucleotides is activated by IR but not UV (27). Our results suggest that this novel pathway might include p48, XPC, gadd45, and PCNA.

Four of the 34 genes play roles in apoptosis (Fas, bbc3, TNF-α, OX40 ligand). The remaining genes may have previously unsuspected roles in the DNA damage response or may be among the estimated set of four falsely detected genes.

The 34 genes most highly ranked by SAM are only a subset of all of the genes that change 1.5-fold with IR. Indeed, we calculated the difference between the number of genes called significant and the number of falsely significant genes for decreasing Δ = 0.3, 0.2, and 0.1, and found the differences to be 92, 170, and 184, respectively. Thus, SAM suggests that approximately 180 of the 6,800 genes on the microarray

were induced or repressed by 5 Gy IR.

Discussion

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SAM is a method for identifying genes on a microarray with statistically significant changes in expression, developed in the context of an actual biological experiment. SAM was successful in analyzing this experiment as well as several other experiments with oligonucleotide and cDNA microarrays (data not shown).

In the statistics of multiple testing (28-30), the family-wise error rate (FWER) is the probability of at least one false positive over the collection of tests. The Bonferroni method, the most basic method for bounding the FWER, assumes independence of the different tests. An acceptable FWER could be achieved for our microarray data only if the corresponding threshold was set so high that no genes were identified. The step-down correction method of Westfall and Young (29), adapted for microarrays by Dudoit *et al.* (http://www.stat.berkeley.edu/users/terry/zarray/Html/matt.html), allows for dependent tests but still remains too stringent, yielding no genes from our data.

Westfall and Young (29) define "weak control" to be control of the FWER when all of the null hypotheses are true (i.e., when there are no changes in gene expression). "Strong control" is control of the FWER when any subset of the null hypotheses is true. Under certain conditions, weak control implies strong control. In fact, the step-down correction method exerts both weak and strong control.

The method of Benjamini and Hochberg (31) assumes independent tests and guarantees an upper bound for the FDR (with both weak and strong control) by a step-up or step-down procedure applied to the individual *P* values. For our data, the *P* value for each gene is calculated from permutations of the eight experiments. Because of the limited number of permutations, the FDR is too "granular", and we identified

either zero or 300 significant genes, depending on how the *P* value was defined. A similar granular result was obtained for the adaptation to dependent tests by Benjamini *et al.* [*The Control of the False Discovery Rate in Multiple Testing Under Dependency* (Department of Statistics and Operations Research, Tel Aviv University, Tel Aviv). http://www.math.tau.ac.il/~ybenja/].

SAM does not have strong or weak control of the FWER. Instead, SAM provides an estimate of the FDR for each value of the tuning parameter Δ. The estimated FDR is computed from permutations of the data and hence assumes that all null hypotheses are true, allowing for the possibility of dependent tests. It seems plausible that this estimated FDR approximates the strongly controlled FDR when any subset of null hypotheses is true. However, we have not proven this in general. It is possible for SAM to give an estimate of the FDR that is greater than 1. However, this has not occurred in our experience. Indeed, SAM provides a reasonably accurate estimate for the true FDR. To confirm this, we constructed artificial data sets in which a subset of genes was induced over a background of noise. SAM successfully identified the induced genes and estimated the FDR with reasonable accuracy.

Although this paper analyzes a simple two-state experiment, SAM can be generalized to other types of experiments by defining $d(i)$ in a different way. Suppose the data includes gene expression $x_j(i)$ and a response parameter y_j in which $i = 1, 2, \ldots, m$ genes, $j = 1, 2, \ldots, n$ states. The generalized statistical parameter still takes the form $d(i) = r(i)/[s(i) + s_0]$, except that the definitions of $r(i)$ and $s(i)$ change.

To identify genes with changes in expression in an experiment with three or more states, the parameter $d(i)$ is defined in terms of the Fisher's linear discriminant. One goal might be to identify genes whose expression in one type of tumor is different from its expression in other types of tumors. Suppose that a set of n samples consists of K nonoverlapping subsets, such that the response parameter $y_{j\varepsilon}\{1, \ldots, K\}$. Define C

$(k) = \{j : y_j = k\}$. Let n_k = number of observations in $C(k)$. The average gene expression in each subset is $\bar{x}_k(i) = \Sigma_{j \in C(k)} x_j(i)/n_k$ and the average gene expression for all n samples is $\bar{x}(i) = \Sigma_j x_j(i)/n$. Then define:

$$r(i) = \{[\Sigma_k n_k/\Pi_k n_k]\Sigma_k n_k[\bar{x}_k(i) - \bar{x}(i)]^2\}^{1/2} \quad [3]$$

$$s(i) = \{[\Sigma_k(1/n_k)/\Sigma_k(n_k - 1)]\Sigma_k\Sigma_{j \in C(k)}[x_j(i) - \bar{x}_k(i)]^2\}^{1/2} \quad [4]$$

SAM can be adapted for still other types of experimental data. For example, to identify genes whose expression correlates with survival time, $d(i)$ is defined in terms of Cox's proportional hazards function, in which some of the patients remain alive or are lost to follow-up at the time of the study. To identify genes whose expression correlates with a quantitative parameter, such as tumor stage, $d(i)$ can be defined in terms of the Pearson correlation coefficient. Another example includes the definition of $d(i)$ for paired data, such as gene expression in tumors before and after chemotherapy. In each case, the FDR is estimated by random permutation of the data for gene expression among the different experimental arms, i.e., permutations among the n arms of y_j. Thus, SAM is a robust and straightforward method that can be adapted to a broad range of experimental situations. SAM and the adaptations discussed above are available for use at http://www-stat-class.stanford.edu/SAM/SAMServlet.

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Abbreviations

SAM, significance analysis of microarrays; FDR, false discovery rate; IR, ionizing radiation; FWER, family-wise error rate.

Footnotes

‡ To whom reprint requests should be addressed. E-mail: chu@cmgm.stanford.edu .

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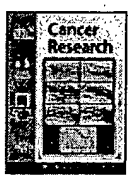

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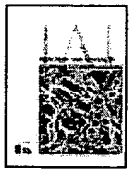

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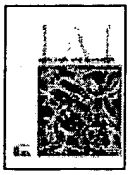

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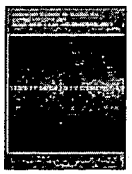

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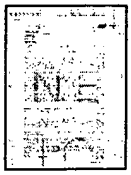

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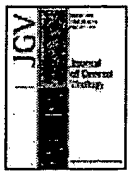

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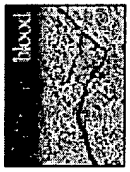

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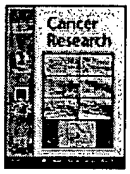

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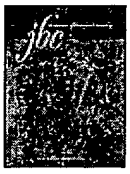

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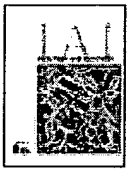

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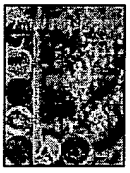

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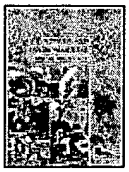

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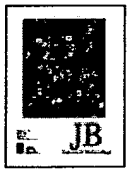

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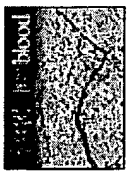

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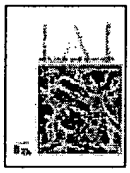

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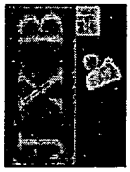

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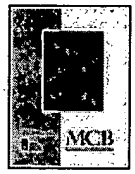

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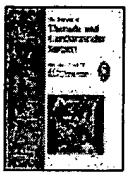

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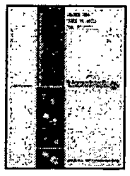

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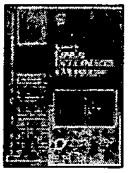

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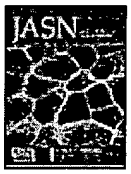

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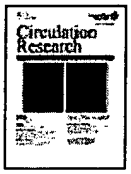

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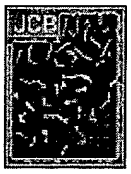

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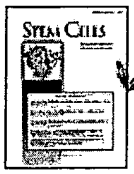

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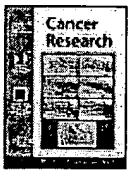

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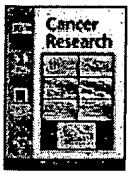

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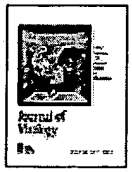

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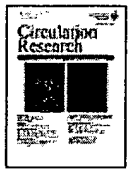

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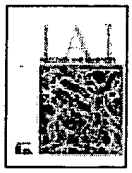

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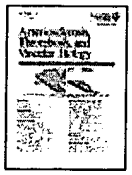

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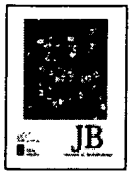

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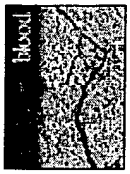

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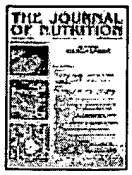

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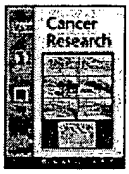

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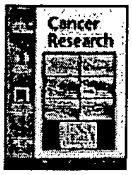

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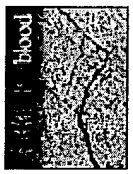

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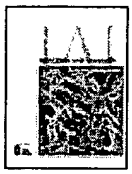

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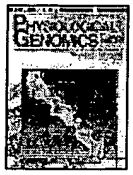

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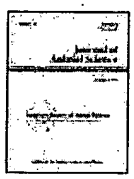

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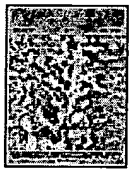

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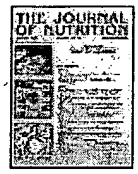

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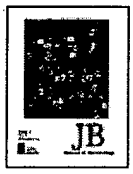

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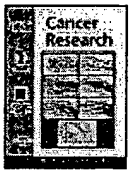

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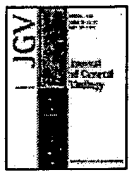

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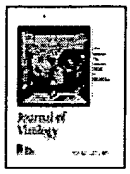

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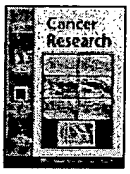

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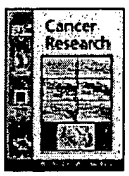

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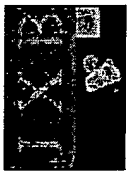

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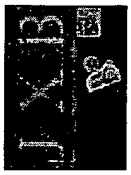

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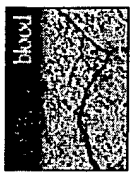

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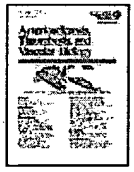

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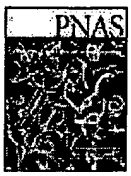

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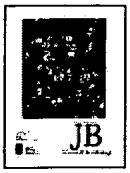

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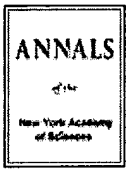

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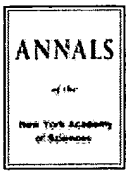

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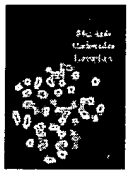

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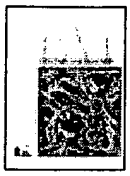

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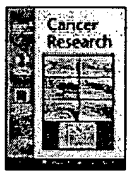

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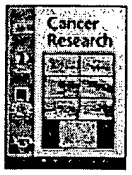

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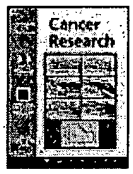

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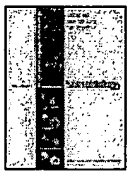

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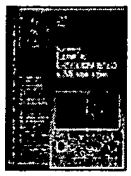

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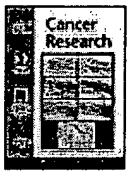

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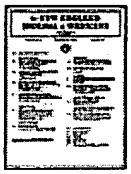

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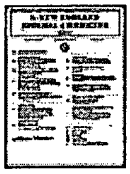

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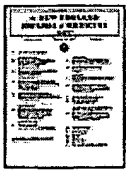

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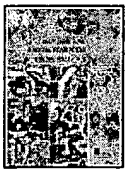

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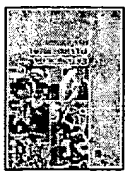

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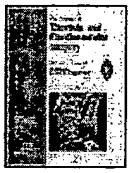

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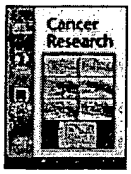

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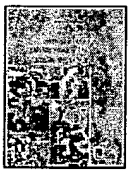

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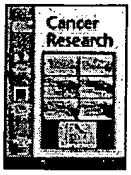

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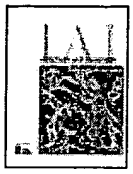

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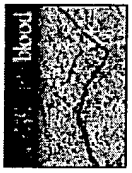

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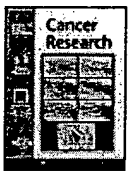

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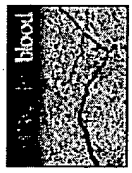

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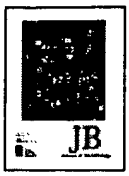

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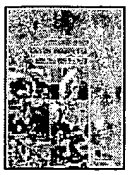

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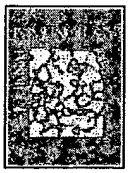

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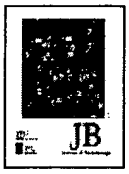

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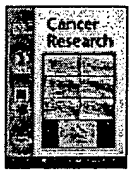

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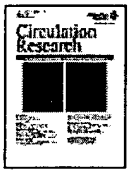

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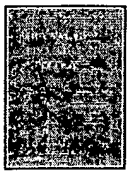

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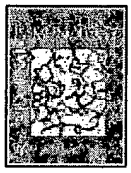

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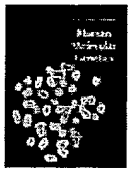

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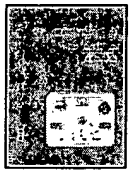

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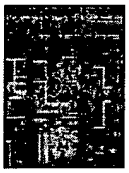

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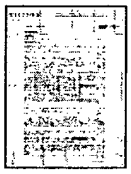

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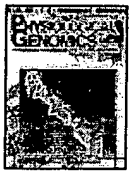

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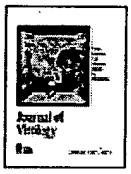

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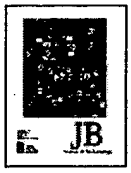

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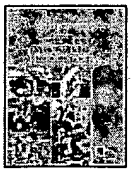

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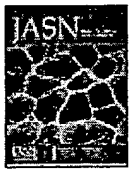

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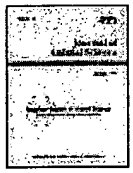

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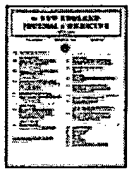

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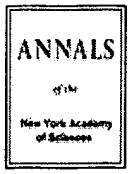

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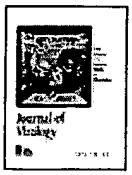

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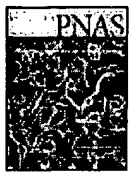

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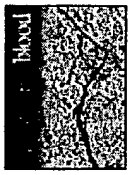

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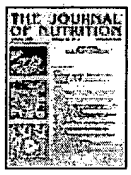

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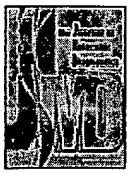

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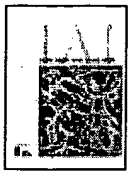

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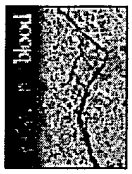

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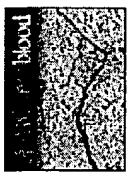

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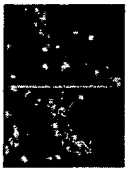

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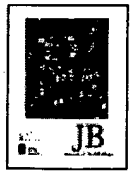

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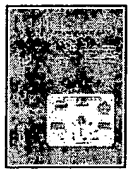

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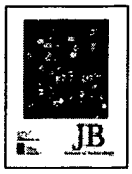

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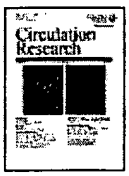

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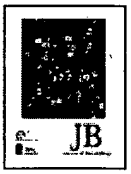

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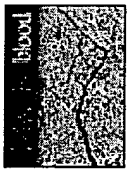

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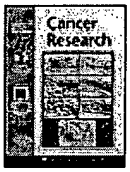

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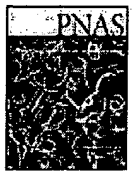

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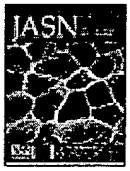

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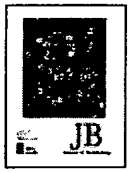

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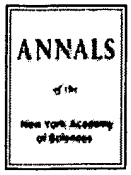

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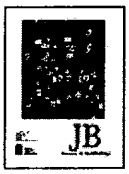

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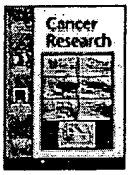

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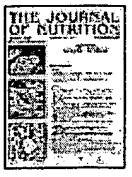

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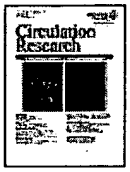

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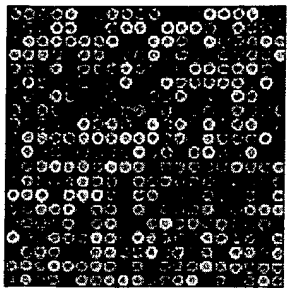
ATTACHMENT 2



SAM: Significance Analysis of Microarrays

Supervised learning software for genomic expression data mining

News

NEW New release 2.20, Oct 4, 2005. SAM now provides sample size assessment-estimates of FDR, FNR, type I error and power for different sample sizes. "A simple method for assessing sample sizes in microarray experiments" (pdf) .

NEW Major New Release: Version 2.0. June 6, 2005. Now version 2.11---- Aug 24, 2005. All users should upgrade to this version. SAM now handles time course data, does non-parametric tests and pattern discovery, It also reports local false discovery rates and miss rates.

A discussion and annoucement group for all SAM-related discussions and announcements has been created. See http://groups.yahoo.com/group/sam-software.

Features

- Developed at Stanford University Labs: based on recent paper of Tusher, Tibshirani and Chu (2001): "Significance analysis of microarrays applied to the ionizing radiation response" (ps file). (pdf version). PNAS 2001 98: 5116-5121, (Apr 24). "Raw data"
- Correlates gene expression data to a wide variety of clinical parameters including treatment, diagnosis categories, survival time and time trends
- Provides estimate of False Discovery Rate for multiple testing
- Convenient Excel Add-in
- Works with data from both cDNA and oligo microarrays. Can also be applied to protein expression data and SNP chip data.
- Patent Pending for SAM technology

- SAM uses the FDR and q-value method presented in Storey (2002) A direct approach to false discovery rates. J. Roy. Stat. Soc. Ser. B, 64:479-498;

  Local false discovery rates proposed in Efron, B., Tibshirani, R., Storey, JD, and Tusher, V. (2001). Empirical Bayes Analysis of a Microarray Experiment, JASA, 96, 1151-1160 and Efron and Tibshirani, Microarrays, Empirical Bayes Methods, and False Discovery Rates" Genet. Epidemiol. 2002 Jun;23(1):70-86;

  and *Miss rates*--- Jon Taylor, Rob Tibshirani and Brad Efron. The ``Miss rate'' for the analysis of gene expression data; Biostatistics 2005 6 (1):111-117.

- List of features
- R package samr
- Sample screens
- Frequently Asked Questions
- ``Samster'' tool
- Euan Ashley's heatmap builder
- Related links: PAM package for microarray classification;
  CGH-Miner package for CGH data;
  PPC package for protein mass spec classification
  Superpc package for microarray prediction;

Obtaining SAM

- Academic users can download SAM by going directly to the registration page. **Please note that this is the full version!**
- Non academic users should first register via the registration page. An evaluation version (limited to 500 genes) can be downloaded directly from that page.

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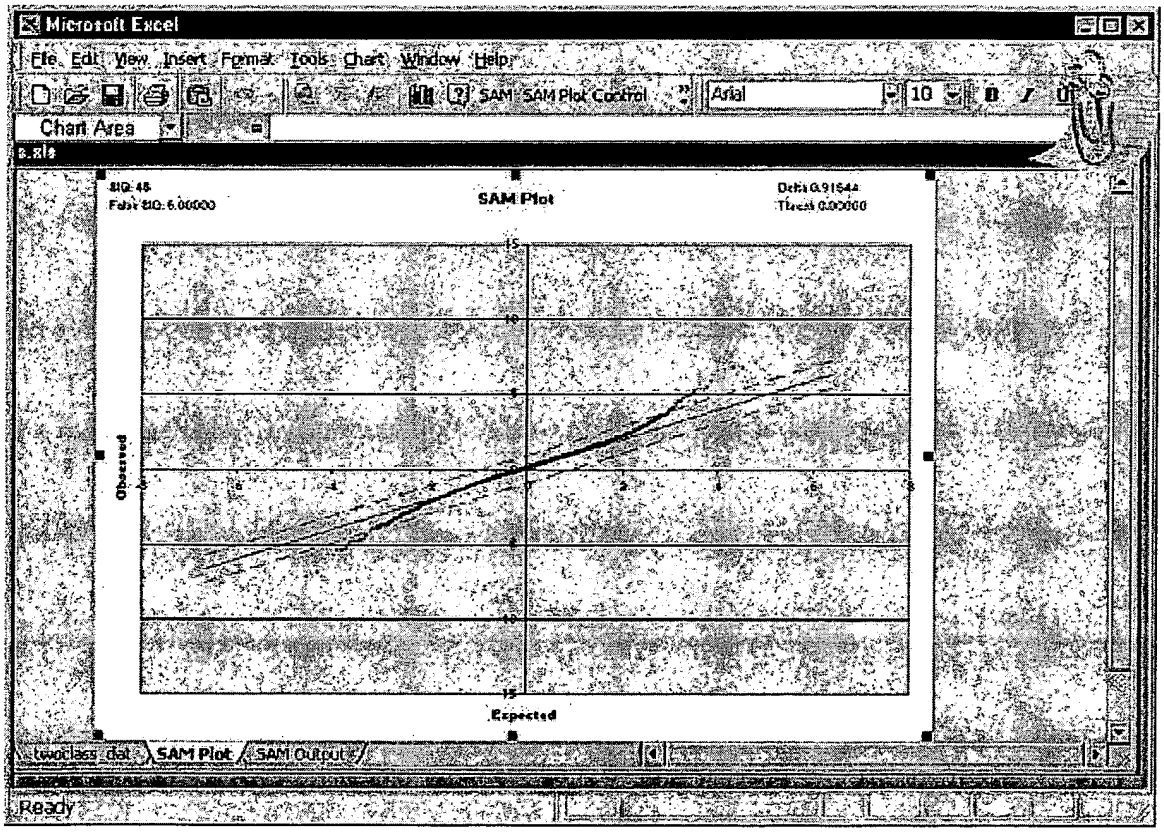

ATTACHMENT 3

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OPEN ACCESS ARTICLE

From The Cover

GENETICS

An expression signature for p53 status in human breast cancer predicts mutation status, transcriptional effects, and patient survival

Lance D. Miller [*,†], **Johanna Smeds** [‡], **Joshy George** [*], **Vinsensius B. Vega** [*], **Liza Vergara** [*], **Alexander Ploner** [§], **Yudi Pawitan** [§], **Per Hall** [§], **Sigrid Klaar** [‡], **Edison T. Liu** [*,†] **and Jonas Bergh** [‡]

[*]Genome Institute of Singapore, 60 Biopolis Street, #02-01, Singapore 138672; [‡]Department of Oncology and Pathology, Radiumhemmet, Karolinska Institute and Hospital, S-17176 Stockholm, Sweden; and [§]Department of Medical Epidemiology and Biostatistics,

Karolinska Institutet, 17177 Stockholm, Sweden

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Perturbations of the p53 pathway are associated with more aggressive and therapeutically refractory tumors. However, molecular assessment of p53 status, by using sequence analysis and immunohistochemistry, are incomplete assessors of p53 functional effects. We posited that the transcriptional fingerprint is a more definitive downstream indicator of p53 function. Herein, we analyzed transcript profiles of 251 p53-sequenced primary breast tumors and identified a clinically embedded 32-gene expression signature that distinguishes p53-mutant and wild-type tumors of different histologies and outperforms sequence-based assessments of p53 in predicting prognosis and therapeutic response. Moreover, the p53 signature identified a subset of aggressive tumors absent of sequence mutations in p53 yet exhibiting expression characteristics consistent with p53 deficiency because of attenuated p53 transcript levels. Our results show the primary importance of p53 functional status in predicting clinical breast cancer behavior.

microarray | expression analysis | tumor profiling | class prediction

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The p53 tumor suppressor is a critical regulator of tissue homeostasis, and its inactivation at the gene or protein level confers cellular properties conducive for oncogenesis and cancer progression. Mutations in p53 occur in >50% of human cancers (1, 2), and the mutational status of p53 is prognostic in many malignancies (3). In breast cancer, p53 mutations are associated with worse overall and disease-free survival, independent of other risk factors (4), and have been implicated in resistance to anticancer therapies (5-11). These observations, however, have been

inconsistent (12, 13), owing, in part, to the variable accuracy of the methods to ascertain p53 status, variation in disease severity attributable to the different forms of p53 mutation, and studies of insufficient size (8, 11, 14). Further confounding the association between p53 status and patient risk is the growing number of alternative molecular mechanisms (e.g., MDM2) that compromise p53 function.

In this study, we explored the possibility that a gene-expression signature, derived from differences between p53 mutant (mt) and wild-type (wt) breast tumors, could provide a more accurate measure of the functional configuration of p53, thereby improving its prognostic utility. Using oligonucleotide microarrays covering >30,000 genes, we analyzed the global transcript levels of 251 primary invasive breast tumors for which we have detailed information on p53 status, as determined by cDNA sequencing (6) and pursued a validation strategy of intersecting alternative array data sets. We found that, in most cases, tumors with mt and wt p53 can readily be distinguished by their expression profiles and that a 32-gene p53 signature is consistently associated with patient survival in different patient subsets, independent of other risk factors, and is a superior prognostic and predictive indicator, compared with p53 mutation status alone.

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Patients and Specimens. Frozen tissue was collected from 315 consecutively presented primary breast cancers representing 65% of all those resected in Uppsala County, Sweden, from January 1, 1987 to December 31, 1989 (6). Of these tissues, 251 were comprised predominantly of diseased tissue, were sequenced for p53 (6), and yielded sufficient RNA for array analysis. Clinicopathological variables measured at diagnosis were obtained from patient records and are described in detail in *Supporting Materials and*

Methods, which is published as supporting information on the PNAS web site. This microarray study was approved by the ethical committee at the Karolinska Institute, Stockholm, Sweden.

Expression Profiling. Total RNA was extracted from samples by using RNEasy Mini kit (Qiagen, Hilden, Germany) and evaluated on a 2100 Bioanalyzer (Agilent Technologies). *In vitro* transcription products were prepared from 2-5 μg of total RNA, hybridized to the Affymetrix U133 A and B arrays and washed and scanned according to the manufacturer's instructions.

Microarray Data Processing. Raw data were normalized by using the global mean method. Probe-set signal values were natural log transformed and scaled by adjusting the mean intensity to a target signal value of log 500. Samples with suboptimal average signal intensities (i.e., scaling factors >3.5) or GAPDH 3'/5' ratios >3.5 were relabeled and rehybridized on new arrays. If visible artifacts were observed, the same cRNA was rehybridized on new chips.

Class Prediction. For gene selection, we fit a linear model to the expression data with expression level as the response and p53 status, estrogen-receptor (ER) status, and grade status as the predictor variables. As an initial filter, we excluded genes with a *P* value for model fit >0.001 and ranked genes in decreasing order of the absolute value of the p53 status coefficient. For class prediction, we evaluated several supervised learning methods, including diagonal linear discriminant analysis (15), *k* nearest neighbors (16), and support vector machines (17), as described in *Supporting Materials and Methods*.

Data Analysis. For all hierarchical cluster analyses, log expression values of each gene were mean centered, and genes and tumors were clustered by using Pearson correlation and average linkage (CLUSTER and TREEVIEW software, http://rana.lbl.gov/EisenSoftware.htm).

The Kaplan-Meier estimate was used to compute survival curves, and the *P* value of the likelihood-ratio test was used to assess statistical significance of the hazard ratios. All patients with contralateral or bilateral cancers were omitted, and patients who died of their cancer 10 years after diagnosis were systematically censored.

For association tests, the x^2 test was used, unless the number of events was <5 in any category, in which case Fisher's exact test was used.

Cox regression was used to confirm the prognostic significance of the p53 classifier in multivariate analyses. The initial model, comprising all conventional predictors, and p53 mutation status and the p53 signature as competing measures of p53 activity, was simplified by using a stepwise model-selection procedure based on the Akaike information criterion. Remaining predictors were assessed by likelihood-ratio test.

Independent Datasets. The Sørlie *et al.* (18) and Chen *et al.* (19) data and clinical annotations were obtained from the Stanford microarray database by using filtering parameters as described by the authors. The Ma *et al.* (20) "whole tumor" data set was downloaded from the Gene Expression Omnibus with accession no. GSE1379 [NCBI GEO] , and each array was mean centered. The van't Veer *et al.* (21) data and survival annotation were accessed through the Rosetta Inpharmatics publications archive. All IMAGE clone IDs or GenBank accession nos. of array probes were mapped to UniGene build no. 167.

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P53 Mutant and WT Tumors Are Molecularly Distinct. Transcript profiles of 251 primary breast tumors were assessed by using Affymetrix U133 oligonucleotide microarrays. Previously, cDNA sequence analysis revealed that 58 of these tumors had p53 mutations

resulting in protein-level changes, whereas the remaining 193 tumors were p53 wt (6). By unsupervised hierarchical cluster analysis, we found that p53 mt and wt tumors are distinguished by pervasive molecular differences. With the top 2,000 most variably expressed genes (selected independent of p53 status), >80% of the p53 mt tumors clustered into one branch and >70% of the p53 wts into the other ($P = 5.6 \times 10^{-13}$; see Fig. 5, which is published as supporting information on the PNAS web site). Importantly, this separation remained highly significant ($P < 2 \times 10^{-12}$) across a range of gene panels from the top 5,000 genes with highest variance to the top 125 (see Table 1, which is published as supporting information on the PNAS web site). This separation was most heavily influenced by three predominant gene clusters comprising genes involved in immune response, proliferation, and estrogen response (Fig. 5). Univariate analysis by statistical analysis of microarrays (SAM) (22) identified 6,545 Affymetrix probe sets representing ≈5,290 distinct genes whose expression patterns distinguished p53 mt and wt tumors with a false discovery rate (q value) <1% and d score (modified t statistic) >2.0 (see Table 2, which is published as supporting information on the PNAS web site), further illuminating the extensive nature of the molecular variation underlying p53 status. Topping the list of genes most highly expressed in p53 mt tumors were those with roles in cell cycle and proliferation, consistent with the observation that wt p53 has a negative regulatory effect on cell-cycle genes. The genes more highly expressed in the p53 wt tumors included uncharacterized genes, signaling molecules and transcription factors, transcriptional targets of p53, and estrogen-inducible genes.

The p53 status was also correlated with two other clinical parameters, ER status and tumor grade (Fig. 5). Within the p53 mt-rich cluster, we observed 89% of ER-negative tumors ($P = 1.9 \times 10^{-10}$), 79% of grade III tumors ($P = 3.8 \times 10^{-11}$), and only 14% of grade I tumors ($P = 2.5 \times 10^{-7}$). The finding that p53 mutant tumors are correlated with ER negativity and grade III status is consistent with previous reports that p53 mutations associate with ER negativity and high tumor grade (23).

A Gene Expression Classifier Predicts p53 Status in Independent Breast and Liver Cancer Data Sets. We considered the possibility that the differential expression observed between p53 mt and wt tumors might, to some extent, reflect changes in the operational configuration of the p53 pathway. We reasoned that some p53 wt tumors would be p53 deficient through mechanisms other than p53 mutation, such as MDM2 amplification or p14/ARF deletion and, thus, possess expression profiles more akin to p53 mt tumors with dysfunctional p53. To explore this possibility, we fitted a multivariate linear regression model (i.e., linear modelfit) (24) that allowed us to rank genes by their correlation with p53 status, while controlling for histologic grade and ER status. As a result, many cell-cycle genes correlated with p53 status by univariate analysis were no longer well associated (see Fig. 6, which is published as supporting information on the PNAS web site), suggesting that the transcriptional profiles of most cell-cycle genes are more related to histologic grade than to p53 status.

For class discrimination, we evaluated several linear learning methods including: diagonal linear discriminant analysis (DLDA) (15), *k*-nearest neighbors (*k*NN) (16), and support vector machines (SVM) (17). In each case, the optimal gene classifier was obtained by leave-one-out cross validation, where the linear model-fit procedure was iteratively applied to all samples minus the left-out sample. The resulting prediction accuracies were highly similar, ranging from 84.9% to 85.7% (see *Supporting Materials and Methods*). Interestingly, 20 tumors were consistently "misclassified" by all three methods (8 wt and 12 mt), indicating a surprising degree of concordance among misclassified tumors. DLDA showed the highest sensitivity for detecting p53 mutants (i.e., 79% sensitivity compared with 53% for both *k*NN and SVM) and was therefore selected for further analysis. By DLDA, the optimal classifier was comprised of 32 genes, whereby 26 of the wt tumors were misclassified as mutant-like, and 12 mutants were misclassified as wt-like (Fig. 1*A*).

To evaluate the performance of the classifier genes (referred to hereafter as the p53

signature genes) as a clinical discriminator of p53 status, we accessed two publicly available cDNA microarray data sets where p53 mutational status was known: a breast cancer study by Sørlie *et al.* (18) and a liver cancer study by Chen *et al.* (19). In the Sørlie data set, 69 breast tumors had been sequenced for p53 mutations. Of our p53 signature genes, 28 mapped to established UniGene IDs, and more than half of these 28 genes were represented on the Sørlie *et al.* microarray. However, only nine were found to correspond to cDNA probes having expression measurements present in >50% of tumors, where the tumors possessed measurements for >50% of genes (resulting in a subset of 44 well sampled tumors). Because the classification rules could not be directly applied, we used this 9-gene subset of the p53 signature to hierarchically cluster the tumors in an unsupervised manner. Fig. 1*B* shows a significant separation of p53 mt and wt tumors: 77% of mutants clustered into one branch, and 77% of wts clustered into the other ($P = 0.0003$). By Monte Carlo simulations, we estimated the probability that a randomly selected nine-gene subset could cluster the samples with equivalent or better significance was $P = 0.008$, thus reaffirming the robust discriminative power of the p53 signature genes.

In the Chen *et al.* liver cancer data set (38), p53 protein levels had been ascertained by immunohistochemistry (IHC). Eight of our signature genes could be mapped to all 59 tumors assayed for p53, with each gene having data present in >90% of all tumors and where each tumor contained data for >50% of the genes. We observed that even this eight-gene subset was able to cluster the liver cancers into two primary clusters significantly correlated with p53 levels: 87% of the IHC-positive (predicted mts) in one cluster, and 61% of the predicted wts in the other ($P = 0.00035$) (Fig. 1*C*). Again, the probability of this clustering occurring by random chance was $P = 0.009$ by Monte Carlo *P* value estimation. Taken together, these observations suggest that the genes comprising the p53 signature are robust in their ability to classify not only breast tumors but also liver cancers according to their p53 mutational status and, therefore, may have generalizable utility in predicting p53 status in a range of cancer types.

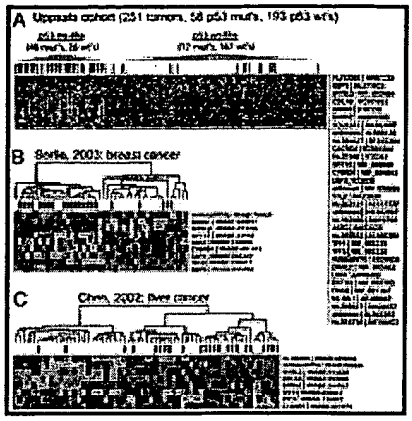

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Fig. 1. The p53 signature is associated with p53 status in independent data sets. Clustergrams are oriented as outlined in Fig. 5. (*A*) Expression profiles of the Uppsala tumors segregated by the 32-gene signature. Unigene symbols and GenBank IDs are listed to the right. (*B*) P53 mt and wt breast tumors from Sørlie *et al.* (18) were clustered by using a nine-gene subset of the p53 signature. (*C*) P53 mt and wt liver tumors (predicted by immunohistochemistry) from Chen *et al.* (19) were clustered by using an eight-gene subset of the p53 signature. Green dendrogram branches denote tumors with the wt-like configuration; red branches indicate those with mt-like profiles. Probe IMAGE clone IDs from the original studies are listed. Black bars denote mt p53 status.

Transcript Analysis of p53 Pathway Genes Corroborates Tumor Classifications. We hypothesized that the p53 expression signature may better reflect the relative intactness of p53 function in the tumor than sequence mutation status alone, implying that p53 sequence-wt tumors "misclassified" as mt-like may, in fact, be p53 deficient by other means. First, we considered the possibility that p53 deficiency could result from reduced p53 transcript levels. We compared the transcript levels of p53 among the different tumor classes (Fig. 2). We observed that the overall expression level of p53 was significantly reduced in the 26 wt tumors with mt-like signatures (referred to henceforth as the "26 mt-like" tumors), compared with the remaining 167 wt tumors classified as wt-like ($P = 1.8 \times 10^{-4}$), strongly suggesting that reduced p53 transcripts can result in biological consequences *in vivo*.

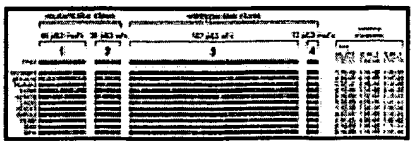

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Fig. 2. Transcript levels of p53 and its transcriptional targets are consistent with classification results. Expression levels of p53-pathway-relevant genes were examined in different tumor subgroups. The

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four tumor subgroups are defined as follows: (*i*) p53 mt tumors classified as mt-like ($n = 46$), (*ii*) p53 wt tumors classified as mt-like ($n = 26$), (*iii*) p53 wt tumors classified as wt-like ($n = 167$), and (*iv*) p53 mt tumors classified as wt-like ($n = 12$). Differences in transcript levels were determine by *t* test and are shown in a summary table to the right; *P* values >0.05 are shown in gray.

We further hypothesized that known transcriptional targets of p53 would show altered transcription in p53-deficient tumors. Indeed, a number of p53 target genes demonstrated expression patterns consistent with a mutant p53 status (Fig. 2). The *TP53*-inducible genes *TP53INP1, SEMA3B, PMAIP1* (*NOXA*), *FDXR, CCNG1*, and *LRDD*, which all contain functional p53-binding sites in their promoters, showed significantly lower expression in the 26 mt-like tumors, compared with the other wt (all at $P < 0.05$). In a consistent manner, all but one of these genes were also significantly reduced in the p53 mt tumors, compared with all wt tumors. Furthermore, in all but two cases, these genes showed significantly higher expression in the set of 12 sequence-mt tumors classified as wt-like when compared with the other mts, suggesting that the p53 mutations in these 12 tumors may have a more benign effect, with respect to p53 functionality. *CHEK1* and *CHEK2* are both upstream effectors of p53 function known to be transcriptionally repressed by p53. Significantly, their mRNA levels were elevated in both the p53 mt and p53 mt-like classes. Again, the 12 mts classified as wt-like showed a reversed pattern, i.e., displaying significantly lower expression of these genes, compared with the other 46 p53 mutants. Together, these observations suggest that the "misclassified" tumors more correctly reflect the active/inactive status of the p53 pathway and are consistent with the notion that reduced p53 levels in breast tumors result in downstream transcriptional changes similar to those found in p53 mutations.

Of note, the canonical marker of p53 activity, CDKN1A (p21/WAF1), was only

moderately higher in p53 wt tumors, compared with those with sequence mutations ($P = 0.02$), and not significantly lower in the 26 mt-like tumors, compared with the other wts ($P = 0.09$; data not shown). Furthermore, the known p53-inducible genes *PERP*, *BAX*, and *SFN* (14-3-3 sigma) were, paradoxically, all expressed at higher levels in the p53 mutants and the 26 mt-like tumors rather than the expected lower levels (Fig. 2). These observations may reflect cross-talk among different transcriptional regulators in the consensus of primary tissues, as compared with dynamic changes in single cell lines. For example, the p53 target genes *p21* and *BAX* are also directly regulated by the breast cancer oncogene, *c-Myc*, in a manner independent of, and antagonistic to, p53 (25, 26). The regulation of p53 target genes by alternative transcriptional modifiers acting independently of p53 or in the context of p53 deficiency (e.g., *PERP*, *BAX*, and *SFN*) may have implications for p53 tumor-suppressor activity.

We next asked whether the mutational spectrum of p53 in our tumors could explain the different functional consequences, as measured by the expression profiles. Of the 46 p53 mt tumors correctly classified as mts, 43% (20 of 46) possessed "severe" mutations, defined as insertions ($n = 2$), deletions ($n = 11$), and stop codons ($n = 7$) resulting in frame shifts and truncations, whereas in the 12 p53 mutants classified as wt-like by the expression signature, only 1 contained a severe mutation, a 3-bp insertion in the DNA-binding domain, resulting in the in-frame addition of a glycine residue. Notably, this difference was statistically significant at $P = 0.02$. Using the IARC TP53 mutation database (ITMD) (27), we cross-compared the missense point mutations (mpms) in each tumor group with the ITMD's index of 418 mutants previously analyzed for dominant-negative function. Only 1 of the 11 mpms among the 12 wt-like mutants had been demonstrated previously to have dominant-negative activity, compared with 12 of 27 within the mt-like group ($P = 0.039$). Together, these data suggest that, at the sequence level, the 12 p53 mutants classified as wt-like may, in fact, represent p53 mutant forms that have less biological effect.

The p53 Signature Predicts Outcome Better Than p53 Mutation Status Alone. We next asked whether the p53 signature could predict disease-specific survival in the patients of the Uppsala cohort. The classifier separated patients into low and high risk groups with a much higher statistical significance than the sequence-based p53 status alone ($P = 0.0006$ versus $P = 0.01$, respectively) (Fig. 3 *A* and *B*). More interestingly, when the classifier was tested on the subset of women with wt p53 by sequence, we again observed a significant separation of patients by survival ($P = 0.02$; Fig. 3*C*), indicating that women with p53 sequence-wt tumors, yet exhibiting the mt-like expression signature, have a greater likelihood of dying from their cancer. Fig. 3*D* shows that the survival curve for this tumor type is highly similar to that of p53 mt tumors classified as mt-like (blue and green curves, respectively), whereas the 12 individuals with p53 mt tumors classified as wt-like do not have significantly unique outcomes.

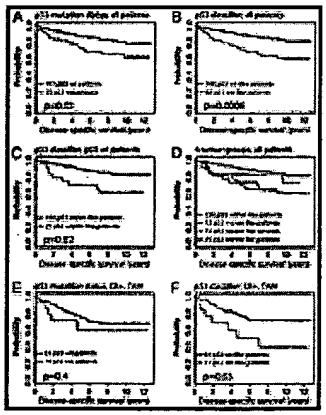

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Fig. 3. The p53 classifier has greater prognostic significance than p53 mutation status alone. Kaplan-Meier survival plots for disease-specific survival are shown for patients classified according to p53 mutation status (*A* and *E*), the p53 classifier (*B*, *C*, and *F*), or both (*D*). All patients were assessed in *A*, *B*, and *D*. Only the patients with p53 wt tumors were assessed in *C*. Sixty-seven ER^+, hormone-treated (TAM) patients were assessed in *E* and *F*.

To further test the clinical utility of the p53 signature, we analyzed its prognostic performance on therapy-specific treatment groups. In a subpopulation of the Uppsala cohort consisting of 67 ER^+ patients who received only adjuvant hormonal therapy

after surgery, the signature was a significant predictor of disease-specific survival (P = 0.05), whereas p53 mutation status alone was not (P = 0.4) (Fig. 3 *E* and *F*). Importantly, by multivariate Cox regression analysis, the p53 classifier remained significantly associated with survival in the hormone-treated group (P = 0.02), the complete cohort (P = 0.02), and the p53 wt group (P = 0.002), even when controlling for the classical predictors (ER and progesterone receptor) and prognostic factors (lymph node status, Elston grade, tumor size, and patient age), whereas the p53 mutation status, as determined by sequencing, did not. This demonstrates that the expression classifier is more directly prognostic of patient survival than is p53 mutation status alone.

The p53 Signature Predicts Outcome in Independent Therapy-Specific Data Sets. We next assessed the prognostic capability of the p53 signature genes in therapy-specific cohorts by using independent microarray data sets from the public domain (Fig. 4; and see Fig. 7, which is published as supporting information on the PNAS web site). First, we evaluated whether the signature genes were prognostic of tumor recurrence in the Ma *et al.* (20) data set of 60 breast tumors derived from patients treated with postoperative radiation and adjuvant tamoxifen monotherapy. In this cohort, patients with and without recurrent disease were matched with respect to tumor grade and tumor node metastasis stage. Twenty-two of the p53 signature genes mapped to 27 probes on the Ma *et al.* spotted oligonucleotide array. Hierarchical cluster analysis with these genes revealed two to three primary tumor clusters with expression profiles that resembled the mt-like and wt-like configurations (Fig. 4*A*). Using these tumor clusters to define patient survival groups, we analyzed disease-free survival (DFS) by the Kaplan-Meier estimate. As shown in Fig. 4 *B* and *C*, the clusters were significantly associated with tumor recurrence [P = 0.01 (two clusters, C1 and C2) and P = 0.005 (three clusters, C1, C2, and C3)]. Thus, concordant results in two independent studies suggest that functional p53 deficiency, as assessed by an expression readout, is predictive of outcome to hormonal therapy.

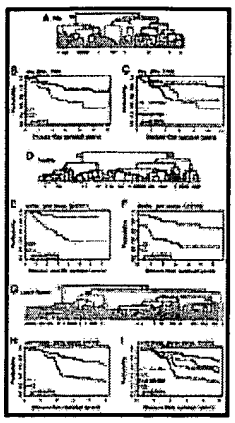

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Fig. 4. The p53 signature predicts survival in independent clinically diverse data sets. (*A*) Tumor dendrogram from clustering 60 tumors and 22 genes (27 probes) from Ma *et al.* (20). (*B* and *C*) Patient subgroups determined by the primary tumor branches (C1-C4) were analyzed for correlations with DFS. (*D*) Tumor dendrogram from clustering 76 tumors and 9 genes from Sørlie *et al.* (18). Patient subgroups defined by the primary tumor branches (C1 and C2) were analyzed for correlations with disease-specific survival (DSS) (*E*) and DFS (*F*). (*G*) Tumor dendrogram from clustering 97 tumors and 21 genes (25 probes) from van't Veer *et al.* (21). (*H* and *I*) Primary tumor clusters (C1-C5) defined patient subgroups for DFS analysis. Red branches denote tumors with the p53 mt-like signature; black branches identify those with the wt-like signature. Black triangles indicate patients who relapsed within 5 years. See Fig. 7 for gene heat maps and probe IDs.

To examine the prognostic performance of the p53 signature genes in patients treated with systemic chemotherapy, we used the Sørlie *et al.* cDNA microarray data set. The majority of patients (>80%) in the Sørlie study received weekly doxorubicin or 5FU and mitomycin and were comprised mostly of late-stage patients (10, 11). Here, the nine-gene partial signature that could distinguish mt and wt tumors with 77% accuracy, was used to hierarchically cluster 76 well sampled tumors with corresponding treatment and survival data (Fig. 4*D*). Again, we observed the tumors cluster into two primary branches with expression patterns characteristic of the wt-like and mt-like configurations. Survival analysis resulted in a highly significant difference in outcome between patients with mt-like and wt-like tumors [$P = 7.5 \times 10^{-5}$ (disease-specific survival) and $P = 5.0 \times 10^{-5}$ (DFS)]; Fig. 4 *E* and *F*) despite the small number of genes used. Notably, Fig. 4*E* predicts a remarkable 5-year 90% survival rate for the 31 p53 wt-like patients, compared with a 35% probability of 5-year survival for the 44 p53 mt-like patients.

Next, we tested the performance of the signature genes on a set of 97 early stage tumors (T1/T2, N0), from patients <55 years of age at diagnosis and treated by radiotherapy alone (21). From our 32-gene signature, we were able to map 25 probes corresponding to 21 signature genes to all 97 tumors with outcome information. Unsupervised clustering revealed two primary and four secondary tumor clusters (Fig. 4*G*) that could significantly discern patients based on time to distant metastasis within a 5-year period [Fig. 4 *H* and *I*; $P = 0.0006$ (two clusters, C1 and C2) and $P = 0.001$ (four clusters, C1, C2, C3, and C4)]. Notably, of the 24 tumors in cluster 1 (C1) that bear the molecular configuration of p53 mt-like tumors, 75% belonged to patients who developed a distant metastasis within 5 years, compared with 26% of 34 patients with tumors comprising C4 (which most closely resemble the p53 wt-like signature). These findings indicate that the p53 signature is also prognostic of recurrence in early stage, locally treated breast cancer.

The p53 Signature Genes Are Not Canonical p53 Targets. To gain some mechanistic insights, we examined the functional annotations of the signature genes for clues to explain their correlations with p53 status and patient outcome. We found that none of the signature genes are known transcriptional targets of p53, nor have they been previously implicated in the p53 pathway. Moreover, promoter analysis revealed no evidence of p53-binding sites. Of the characterized genes, a number are associated with cell growth and proliferation (*MYBL2, TFF1, BRRN1, CHAD, SCGB3A1, DACH*, and *CDCA8*), transcription (*LAF4, NY-BR-1, DACH*, and *MYBL2*), ion transport (*CACNG4, CY-BRD1*, and *LRP2*), and breast cancer biology (*SCGB3A1, TFF1, STC2, NY-BR-1*, and *AGR2*). Interestingly, *MYBL2*, which was transcriptionally up-regulated in the p53 mt-like tumors, is a growth-promoting transcription factor structurally related to the *c-MYB* oncogene. *MYBL2* maps to a chromosomal region frequently amplified in breast cancer (20q13) and has previously been reported to be overexpressed in breast cancer cell lines and sporadic ovarian carcinomas (28, 29). *SCGB3A1* (*HIN1*), which we observed to be down-regulated in the p53 mt-like tumors, is a putative tumor-

suppressor gene that can inhibit breast cancer cell growth when overexpressed and has been found to be transcriptionally silenced by promoter hypermethylation in early stages of breast tumorigenesis (30). Thus, some of the p53 signature genes may contribute mechanistically to the poor prognosis associated with the p53 mt-like tumors.

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Breast cancers are characterized by multiple genetic alterations that, together, comprise the genotype that dictates tumor behavior. It is therefore reasonable that the compilation of genetic changes is a better indicator of clinical behavior than a single gene. Herein, we show that an expression signature, deduced from differences in the molecular configurations of p53 wt and mt tumors, predicts for p53 functional inactivation in primary breast cancers and provides a more accurate and useful measure of p53 clinical functionality than p53 mutation status alone. We show that, in independent data sets of both breast and liver cancers and regardless of other clinical features, subsets of the p53 signature can predict p53 status with significant accuracy. As a predictor of disease-specific survival, we found that the signature significantly outperformed p53 mutation status in a large patient cohort with heterogeneous treatment. Importantly, the p53 signature could significantly distinguish patients having more or less benefit from specific systemic adjuvant therapies and locoregional radiotherapy. Recently, Ma *et al.* identified by microarray analysis two genes (*HOXB13* and *IL17RB*) whose expression ratio was predictive of tamoxifen response. Notably, we found that these genes were also predictive of disease-specific survival in the 67 Uppsala patients treated with tamoxifen monotherapy ($P < 0.01$; data not shown). However, these genes were not prognostic of recurrence in the van't Veer data set, nor were the van't Veer 70 genes prognostic of recurrence in the Ma data set (20),

suggesting that tumor stage and/or therapeutic context is an important determinant of the prognostic capacity of some genes. In contrast, we demonstrate that the p53 signature genes are robustly prognostic of survival and recurrence in both early and late stage disease and in different therapeutic settings.

Although the p53 pathway may be compromised at some level in most human cancers, our analysis of genes involved in the p53 pathway suggests that the p53 expression signature defines some operational configuration of this pathway in breast tumors (more so than p53 mutation status alone) that impacts patient survival and therapeutic response. Recent evidence suggests that tumor sensitivity to some anti-cancer agents may depend largely on the relative intactness of p53-dependent mechanisms of apoptosis (7, 8, 10, 11) and that taxols (microtubule stabilizers), in particular, may have greater efficacy against p53-mt breast tumors than anthracycline-based (genotoxic) compounds (9). Whether the p53 classifier genes identified here are involved in some aspect of this p53 function or will have robust clinically utility as a predictor of therapeutic response warrants further investigation.

Other studies have elucidated gene expression signatures prognostic of breast cancer outcomes (21, 31). Although a 21-gene subset of our p53 signature could significantly distinguish patients with recurrent and nonrecurrent disease in the van't Veer study (21), none of these genes were found to overlap with the 231 genes identified as prognostic discriminators in the van't Veer set; and only one of the classifier genes, *MYBL2*, was found in the Sotiriou 485 survival-correlated genes (31). Similarly, none of the p53 signature genes were found in the top 25 relapse-associated genes reported by Ma *et al.* Thus, the p53 signature genes identified here represent a previously unrecognized prognostic cassette.

In cancer, it is clear that not all p53 mutations have equal effects; some simply confer loss of function, whereas others have a dominant-negative effect (such as

transdominant suppression of wt p53 or oncogenic gain of function), whereas still others show only a partial loss of function where, for example, only a fraction of p53 target genes are dysregulated (32, 33). For these reasons, no single molecular assessment of p53 status appears to provide an absolute indication of the complete p53 function. Although the p53 classification method developed here seeks to categorize all tumors as either p53-deficient or not, it is likely that intermediate types exist with partial p53 functionality, distinguished by expression patterns that fall between those of the predominant mt-like and wt-like classes. Further investigation will be required to resolve the biological and clinical implications of such intermediate tumor classes.

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Footnotes

Freely available online through the PNAS open access option.

Abbreviations: DFS, disease-free survival; ER, estrogen receptor; mt, mutant; wt, wild type.

† To whom correspondence may be addressed. E-mail: millerl@gis.a-star.edu.sg or liue@gis.a-star.edu.sg .

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OPEN ACCESS ARTICLE

MICROBIOLOGY

Ancestral antibiotic resistance in *Mycobacterium tuberculosis*

Rowan P. Morris [*,†], Liem Nguyen [†,‡], John Gatfield [†], Kevin Visconti [*], Kien Nguyen [†§], Dirk Schnappinger [¶], Sabine Ehrt [¶], Yang Liu [*], Leonid Heifets [||], Jean Pieters [†], Gary Schoolnik [*] and Charles J. Thompson [†,‡,]**

[*]Departments of Medicine and of Microbiology and Immunology, Division of Infectious Diseases and Geographic Medicine, Stanford Medical School, Stanford, CA 94305; [†]Biocentre, University of Basel, Klingelbergstrasse 50/70, CH-4056 Basel, Switzerland; [‡]University of British Columbia, Life Sciences Centre, 2350 Health Sciences Mall, Vancouver, BC, Canada V6T 1Z3; [¶]Department of Microbiology and Immunology, Weill Graduate School of Medical Sciences, Cornell University, New York, NY 10021; and

[||]National Jewish Medical and Research Center, Denver, CO 80206

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Chemotherapeutic options to treat tuberculosis are severely restricted by the intrinsic resistance of *Mycobacterium tuberculosis* to the majority of clinically applied antibiotics. Such resistance is partially provided by the low permeability of their unique cell envelope. Here we describe a complementary system that coordinates resistance to drugs that have penetrated the envelope, allowing mycobacteria to tolerate diverse classes of antibiotics that inhibit cytoplasmic targets. This system depends on *whiB7*, a gene that pathogenic *Mycobacterium* shares with *Streptomyces*, a phylogenetically related genus known as the source of diverse antibiotics. In *M. tuberculosis*, *whiB7* is induced by subinhibitory concentrations of antibiotics (erythromycin, tetracycline, and streptomycin) and *whiB7* null mutants (*Streptomyces* and *Mycobacterium*) are hypersusceptible to antibiotics *in vitro*. *M. tuberculosis* is also antibiotic sensitive within a monocyte model system. In addition to antibiotics, *whiB7* is induced by exposure to fatty acids that pathogenic *Mycobacterium* species may accumulate internally or encounter within eukaryotic hosts during infection. Gene expression profiling analyses demonstrate that *whiB7* transcription determines drug resistance by activating expression of a regulon including genes involved in ribosomal protection and antibiotic efflux. Components of the *whiB7* system may serve as attractive targets for the identification of inhibitors that render *M. tuberculosis* or multidrug-resistant derivatives more antibiotic-sensitive.

multidrug resistance | *Streptomyces* | WhiB | microarray | gene expression

The World Health Organization has estimated that between 2000 and 2020, nearly one billion people will be newly infected, 200 million people will get sick, and 35 million will die from tuberculosis (TB) (1). It is the remarkable antibiotic tolerance of the infectious agent *Mycobacterium tuberculosis* to many commonly used broad-spectrum antibiotics that limits chemotherapeutic options and is the root cause of all treatment failure (2). Tolerance may reflect physiological adaptations that occur within the host, perhaps including an undefined developmental or physiological state that underlies persistent infection (3). As a result, patients must be treated with multiple antibiotics for 6-12 months. Patient noncompliance or inadequate drug dosage favors the sequential acquisition of mutations providing resistance and the emergence of multidrug-resistant *M. tuberculosis* strains. In contrast to acquired resistance, intrinsic resistance in *Mycobacterium* has largely been attributed to its impermeable mycolic acid-containing cell envelope (4, 5) that is not found in many other Actinomycetes including *Streptomyces*. However, Jarlier and Nikaido (4) have also pointed out that this permeability barrier is insufficient to fully explain the high levels of drug resistance in *Mycobacterium*, suggesting that there must be synergistic systems effective against drugs that penetrate this barrier. Indeed, several mycobacterial genes not involved in outer envelope assembly confer resistance to specific, broad-spectrum antibiotics (6-8).

Although the best-known *Mycobacterium* species are pathogenic, most are ubiquitous environmental saprophytes belonging to the Actinomycete taxon (9). The taxon also include *Streptomyces* species, filamentous bacteria known for their extraordinary capacity to produce thousands of diverse antibiotics as a part of a developmental program leading to sporulation. Antibiotic biosynthetic genes are found in clusters that typically include the corresponding resistance genes to provide self-protection (10). However, as in other bacteria, genes scattered throughout the genome that may have alternative physiological roles can also confer antibiotic resistance (11). Intuitively, the protective activity of these resistance genes should be a prerequisite for the evolution

of antibiotic biosynthetic pathways.

Indeed, at sublethal concentrations, antibiotics can induce a wide variety of genes, many not known to provide antibiotic resistance (12-14). The expression of some of these antibiotic-induced genes is under the control of stress inducible systems that respond to (13) or lead to (15) decreases in growth rate. The underlying control elements that affect antibiotic resistance include general stress-responsive sigma factors (16) and transcriptional activator proteins of the AraC family (MarA, SoxR, and Rob) (17), as well as genetic systems that provide for more specific adaptation to DNA damage (15) or oxidative stress (8). Such systems are commonly found in diverse bacterial groups and typically modulate antibiotic resistance within a rather narrow concentration range (8, 17). Here we describe a multidrug-resistance system that apparently evolved in the ancestors of antibiotic producing bacteria, which has been retained in saprophytes and pathogens belonging to the Actinomycete taxon.

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Media and Strains. *Streptomyces lividans* 1326 was grown in the nutrient-rich liquid media YEME and cultivated on NE solid media (18). The slow growing mycobacteria *Mycobacterium bovis* bacillus Calmette-Guérin, *M. tuberculosis* H37Rv, and the clinical *M. tuberculosis* isolate 1254 were propagated in 7H9 media (19), supplemented with 10% ADS (5% BSA/2% dextrose/0.8% sodium chloride).

Plasmid Constructions and Mutant Analyses. Annotated *whiB7* ORFs were deleted in the genomes of *S. lividans* and *Streptomyces coelicolor* (nucleotide coordinates 5,647,587-5,648,293; http://jic-bioinfo.bbsrc.ac.uk/streptomyces/ScoDB), *M. tuberculosis* H37Rv (nucleotide coordinates 3,568,405-3,568,801; http://genolist.pasteur.fr/TubercuList), and *M. bovis* bacillus Calmette-Guérin

(nucleotide coordinates 3,523,346-3,522,950; http://genolist.pasteur.fr/BoviList) as described *Supporting Text* and *Data Set*, which are published as supporting information on the PNAS web site. Corresponding ORFs were expressed from vector promoters.

Mycobacterial Survival in Monocytes. Resting or activated J774 monocytes were grown in DMEM/FCS. Monocytes were exposed to *Mycobacterium bovis* bacillus Calmette-Guérin and the corresponding *whiB7* mutant at a multiplicity of one. Activation was achieved by 16-h exposure to 500 units/ml IFN-γ followed by 4-h exposure to both IFN-γ and 1 μg/ml LPS. The monocytes were washed twice with PBS and incubated for 45 min at 37°C/5% CO_2 with amikacin (200 μg/ml). Cells were again washed twice in PBS and incubated in DMEM/FCS. Survival was determined at the indicated incubation times by bacterial incorporation of tritiated uracil followed by liquid scintillation counting (20). For antibiotic susceptibility testing, the infected monocytes were incubated in the presence of indicated spectinomycin concentrations for 48 h before permeabilization and mycobacterial labeling (see *Supporting Text* for details).

Microarray Expression Profiling and Analysis. Labeling of RNA and hybridizations to 70-mer oligonucleotide-based microarrays (Operon) was performed as described (21). Microarrays were scanned by using GenePix 4000A (Axon Instruments). Fluorescence intensities of the two channels at each spot were quantified by using the SCANALYZE software (http://rana.lbl.gov/EisenSoftware.htm). After data for each array were normalized (21), expression ratios were averaged from two biological replicates for antibiotic-induced cultures or from three cultures for the mid-log comparison, and with two microarrays for each of the biological replicates. Data from each experimental condition was analyzed separately by using SIGNIFICANCE ANALYSIS OF MICROARRAYS (22) with a false discovery ratio ≤0.3%. Significantly regulated genes for all experimental conditions were combined to generate a data set containing 2,879 genes. Within this

list, gene expression data could be present for one experimental condition and absent from another. To aid hierarchical clustering, these genes were then filtered to include those that were present across 95% of the 25 experimental conditions (total number of rows in Fig. 3 *b-d*) and a differential expression >2-fold under at least three of these conditions. The resulting 880 filtered genes were organized according to their expression profiles by average linkage clustering using GENESIS software (http://genome.tugraz.at/Software/GenesisCenter.html).

Analysis of Mycobacterial RNA with Quantitative Real-Time RT-PCR. Real time PCR to confirm microarray analysis of *in vitro* grown cultures was performed by using SYBR green (Applied Biosystems). A standard curve was generated for the relative quantification of all genes, and a control reaction lacking reverse transcriptase was performed for every RNA sample. The major housekeeping sigma factor gene *sigA* was used to normalize mRNA levels. Gene induction values were calibrated by comparison with the reference RNA isolated for each experiment.

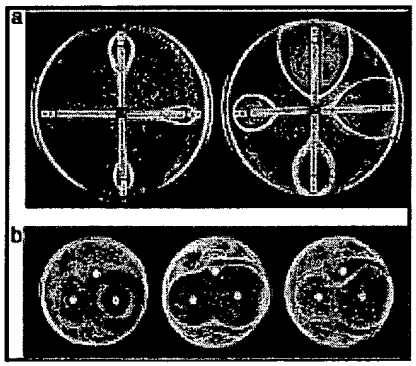

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Fig. 1. Identification of *whiB7*, a gene providing intrinsic antibiotic resistance in *Streptomyces*. (*a*) Antibiotic susceptibility of the wild-type *S. lividans* strain (*Left*) and the spontaneous *whiB7* mutant RM1 (*Right*). Etest strips were applied to seeded spores, and minimal inhibition concentration values were read from the scale (μg/ml) at the point of intersection between inhibition ellipse edge and the strip. Upper, erythromycin; right, tetracycline; lower, rifampicin; left, quinupristin/dalfopristin. (*b*) *S. lividans* RM1 was engineered to allow thiostrepton-inducible expression of *whiB7* by using the expression plasmid pIJ8600. Seeded spores of *S. lividans* wild-type/pIJ8600 (*Left*), the *whiB7* mutant RM1/pIJ8600 (*Center*), or RM1/pIJ8600::*whiB7* (*Right*) were exposed to radial gradients by discs containing 100 μg of oleandomycin

(left), chlorotetracycline (right), or thiostrepton (top). The high frequency of suppressor colonies in the RM1/pIJ8600::*whiB7* culture are presumed to be promoter-up mutants that allow unregulated *whiB7* expression. Tetracycline induced synthesis of a red pigment (likely to be the antibiotic undecylprodigiosin) in both wild-type *S. lividans* and the *whiB7* mutant.

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Identification of a Multidrug Resistance Regulator in *Streptomyces*. We isolated a spontaneous mutant of *S. lividans*, RM1, that was hypersensitive to a diverse array of chemically and functionally unrelated clinical antibiotics that it does not synthesize, including chloramphenicol, fusidic acid, imipenem, lincosamides (clindamycin and lincomycin), macrolides (erythromycin, oleandomycin, and spiramycin), rifampicin, streptogramins (pristinamycin and virginiamycin), and tetracycline (see Fig. 5, which is published as supporting information on the PNAS web site). Sensitivities of the mutant and wild-type parent were quantified by using Etest diffusion strips to compare their minimal inhibition concentrations to four structurally and functionally distinct classes of antibiotics. RM1 was 600-, 400-, 25-, and 40-fold more sensitive to erythromycin, tetracycline, rifampicin, and the pristinamycin derivatives quinupristin/dalfopristin, respectively (Fig. 1*a*). The mutant displayed large decreases in intrinsic antibiotic resistance, but its susceptibility to a variety of other toxic, nonantibiotic stresses, including detergents, antiseptics, and oxidative stress inducers, was unchanged (Fig. 6, which is published as supporting information on the PNAS web site). Standard cloning, sequencing, and site-directed mutagenesis experiments (described in *Supporting Text*) identified the gene responsible for this multidrug resistance as *whiB7* in both *S. lividans* (GenBank accession no. AF205848 [GenBank]) and *S. coelicolor* genomes

(Fig. 2) (23). Sequence comparison of the wild-type locus to that of RM1 revealed a frame shift in the *whiB7* gene resulting from the insertion of a cytosine at nucleotide position 239. This locus was not linked to any recognizable antibiotic biosynthetic cluster. *whiB7* encodes a 122-aa protein related to *whiB*, a putative *S. coelicolor* transcriptional regulatory gene (24). In *M. tuberculosis*, a WhiB-like protein (WhiB3) may act as a transcriptional regulator by binding and modulating the activity of RpoV (SigA), the principle sigma factor in *M. tuberculosis* (25). To further demonstrate the correlation of *whiB7* transcriptional activity with antibiotic resistance, the *S. lividans* mutant RM1 was engineered to allow inducible expression (26) of a wild-type copy of *whiB7*. Fig. 1*b* shows that the circular zones of inhibition caused by diffusion of tetracycline (an aromatic polyketide) or oleandomycin (a macrolide) were distorted and reduced by a radial gradient of the inducer (thiostrepton), indicating higher levels of resistance associated with increased *whiB7* transcription.

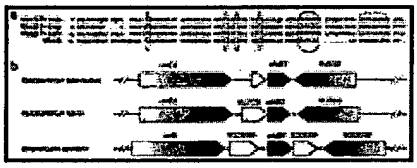

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Fig. 2. The orthologous *whiB7* loci of *Streptomyces* and *Mycobacterium*. (*a*) Alignment of the WhiB7 proteins from both *Mycobacterium tuberculosis* (WhiB7-tub) and *leprae* (WhiB7-lep) with the *Streptomyces* WhiB7 and the prototypic family member WhiB from *Streptomyces coelicolor*. Four absolutely conserved cysteine residues and a tryptophan-containing/glycine-rich motif are conserved throughout the WhiB family (circled). An A/T-Hook DNA binding consensus sequence is found only in WhiB7 paralogs. ~, N-terminal sequence not shown. (*b*) Gene organization of the *whiB7* genomic region. Shaded block arrows represent conserved ORFs.

Members of the *whiB* gene lineage, including *whiB7* of *S. lividans* (alternatively named *wblC*), are restricted to the Actinomycetes (27); BLAST searches did not identify orthologs in any other published bacterial genome sequences. The prototype of this

gene family, *whiB*, was identified as a developmental gene in *Streptomyces* species that is essential for the differentiation of mycelium into pigmented spores (*white*) (28). The family signature is defined by four absolutely conserved cysteines that form an oxygen sensitive iron sulfur cluster (ref. 29 and L.N., P. Jensen, R.P.M., M. Folcher, S. Durr, S. Grzesiek, and C.J.T., unpublished data), and a tryptophan within a glycine-rich sequence (Fig. 2*a*). In addition, *whiB7* paralogs also encode a C-terminal "A/T Hook" domain that is known to bind AT-rich DNA sequences. Although the *M. tuberculosis* genome encodes seven *whiB*-like genes (*whiB1-7*), both homology and synteny predict a minimal core of five orthologous *whiB*-like genes common to *M. tuberculosis, Mycobacterium leprae*, and *Streptomyces* species (*whiB1-4* and *-7*). TBLASTN searches of the 201 completed bacterial genomes identified *whiB7* orthologs in all species of *Streptomyces* (*S. coelicolor* and *Streptomyces averimidilus*), *Mycobacterium* (*tuberculosis* H37Rv, *tuberculosis* CDC1551, *bovis* AF2122/97, *leprae* TN, *avium subsp. paratuberculosis*), and *Nocardia* (*farcinica* IFN10152. The role of the streptomycete *whiB7* gene in determining broad spectrum drug resistance, predicted that it might play a similar role in pathogenic *M. tuberculosis*.

A *whiB7* Ortholog Controls Multidrug Resistance in *M. tuberculosis*. Intrinsic resistance in *M. tuberculosis* could be partially due to a *whiB7* ortholog that is able to provide resistance to antibiotics that have penetrated the cell envelope and entered the cytoplasm. To test this hypothesis, we constructed a gene replacement mutant in *M. tuberculosis*, strain H37Rv. The mutant grew normally, but was defective in its resistance (Table 1) to a variety of antibiotics including macrolides, a lincosamide, and an aminoglycoside. The *whiB7* gene was cloned into the integrative vector pMV361 to provide expression from a strong constitutive promoter (hsp60). Integration of this plasmid (pRPM251) into the chromosome of the *M. tuberculosis whiB7* mutant restored normal, or slightly elevated levels of antibiotic resistance (Table 1). Multidrug sensitivity also resulted from disruption of the *whiB7* gene of the fast growing saprophytic *Mycobacterium smegmatis* (R.P.M. and C.J.T., unpublished results).

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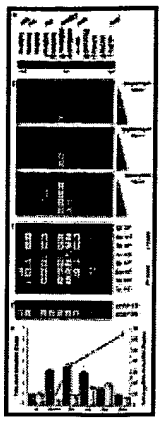
Table 1. Multidrug resistance in *M. tuberculosis* determined by *whiB7*

Induction of the *M. tuberculosis whiB7* Gene by Multiple Antibiotics and Fatty Acids. Antibiotic resistance genes typically confer resistance to one class of antibiotic and are specifically activated by the corresponding drugs. Experiments were carried out to determine whether the broad spectrum of resistance conferred by *whiB7* might be controlled by regulatory systems that are responsive to dissimilar drugs (30). Microarray transcript profiling of all annotated *M. tuberculosis* genes was used to monitor expression in response to three chemically distinct classes of common antibiotics: the frontline antimycobacterial drug streptomycin, as well as erythromycin and tetracycline (Fig. 3*b*). *M. tuberculosis* 1254 cultures were treated with five concentrations of each antibiotic, spanning three orders of magnitude (0.5-100 μg/ml) including the minimal inhibition concentration. Expression was assayed 15 min after exposure to maximize detection of genes whose regulation most directly reflected *whiB7* activity, rather than downstream pleiotropic effects. *whiB7* expression was significantly induced by subinhibitory concentrations of both erythromycin (1.0 μg/ml) and tetracycline (0.5 μg/ml) and also higher levels of streptomycin (25 μg/ml). After longer exposure (24 h), concentrations of streptomycin as low as 1 μg/ml induced *whiB7* (Fig. 3*c*). The levels of induction were dose dependent for all three antibiotics (Fig. 3*b*). Activation of *whiB7* transcription by tetracycline (1 μg/ml) was confirmed by quantitative RT-PCR showing that *whiB7* RNA levels progressively increased ≈70-fold during 24 h of exposure (Fig. 3*e*).

Fig. 3. Identification of antibiotic resistance genes as parts of the *M. tuberculosis whiB7* regulon. Significantly altered gene



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expression ratios from all experiments were averaged, $\log_2$ transformed, and clustered according to the displayed color code. Red and blue indicate higher and lower gene expression, respectively, in experimental samples, in comparison to the reference. Black represents no difference. (*a*) Genes of the *whiB7* regulon. Rv and ORF numbers designate annotated *M. tuberculosis* genes, and arrows indicate contiguous genes. (*b*) Treatment (15 min) of *M. tuberculosis* 1254 with 0.5, 1.0, 5, 25 and 100 μg/ml of erythromycin, streptomycin, and tetracycline. (*c*) Extended antibiotic treatment for 2 and 24 h (1 μg/ml). (*d*) *M. tuberculosis* H37Rv was used as reference and compared to a *whiB7* null mutant (WhiB7 KO) and a H37Rv strain engineered to overexpress *whiB7* (WhiB7 OV). Cells were assayed at an optical density of 0.4 at 600 nm. (*e*) *whiB7* induction by fatty acids. Quantitative RT-PCR-determined induction factors of *whiB7* expression. Primary *y* axis: *M. tuberculosis* grown in MDG fed 50 μM palmitic acid (purple) or its unsaturated form, oleic acid (gray). Secondary *y* axis: induction to prolonged exposure of tetracycline (connected dots) (≈2 μM, 1 μg/ml).

Many antibiotics, including erythromycin and tetracycline, are based on polyketides, fatty acid-like molecules with carbon backbones synthesized by enzyme complexes similar to fatty acid synthase. Like antibiotics, many fatty acids are known to suppress growth of diverse bacteria (31), including *Mycobacterium spp.* (32). Palmitic acid, as well as an unsaturated derivative, oleic acid, were likewise tested for their abilities to induce *whiB7* transcription by quantitative RT-PCR. Although both fatty acids activated *whiB7* transcription, the palmitic acid response was more rapid and achieved higher levels of induction. Although induction kinetics were concentration dependent, at least for the antibiotics tested, higher concentrations of externally applied palmitic acid were needed and lower levels of maximal induction were achieved (3- to 4-fold compared to 70-fold for tetracycline).

In conclusion, *whiB7* expression was progressively induced at the transcriptional level

by sublethal concentrations of antibiotics and fatty acids. Up-regulation of *whiB7* expression may be required for the induction of other genes that could plausibly provide antibiotic resistance. These observations suggested that *whiB7* encoded a regulator whose transcriptional induction activated a regulon providing intrinsic antibiotic resistance.

Identification of Genes in the *whiB7* Regulon by Microarray Analyses. To determine whether the induction of *whiB7* was correlated with the expression of genes associated with antibiotic resistance, microarray expression profiles of mid-log phase cultures of the *whiB7* deletion mutant and a strain overexpressing *whiB7* were compared to parental strain *M. tuberculosis* H37Rv (Fig. 3*d*). These global analyses (details not presented) showed that *whiB7* was the only gene induced initially, after exposure to minimal concentrations of antibiotic (0.5 mg/ml tetracycline for 15 min, for example). Thus, *whiB7* represented a primary regulatory gene whose expression was followed by transcription of other genes in its regulon. Average distance hierarchical clustering identified 12 significantly regulated genes (SAM false discovery rate ≤ 0.3%) whose expression profile appeared to be influenced by antibiotic exposure and the activity of *whiB7* (Fig. 3). The *whiB7*-dependent set of eight transcripts includes three genes that may provide intrinsic antibiotic resistance: *tap* (Rv1258c), encoding an efflux pump that confers low-level resistance to aminoglycosides and tetracycline (33); an unstudied ORF encoding a putative macrolide transporter (Rv1473) with an ATP-binding cassette; and *erm* (Rv1988), homologous to ribosomal methyltransferases and conferring MLS (macrolide, lincosamide, and streptogramin) resistance by modification of 23S rRNA (7, 34). Although the *whiB7* regulon may include unrecognized antibiotic resistance determinants, other functions were also suggested. These include *eis* (Rv2416C), a putative acetyl-transferase providing enhanced survival within macrophages, Rv0263C, a putative carboxylase catalyzing urea degradation, and *cut2*, a putative cutinase/lipase that is reported to be exposed on the outside of the cell membrane and potentially able to release fatty acids from external lipids (35). These

possible functions of other genes in the putative *whiB7* regulon, not known to be antibiotic resistance determinants, require further investigation. Some may play roles in bacterial physiology, a recognized but not well understood determinant of antibiotic resistance (36).

Quantitative RT-PCR was used to independently confirm the induction data for genes within the *whiB7* regulon, including Rv1258, Rv1473, and Rv1988. Furthermore, primers targeting an intergenic sequence upstream of *whiB7* showed that *whiB7* was transcriptionally coupled to the small upstream unannotated ORF, ORFD0316 (Fig. 7, which is published as supporting information on the PNAS web site). Strains engineered to constitutively express *whiB7* in trans (whiB7 OV) were associated with elevated levels of ORFD0316 transcription, and ORFD0316 was down-regulated in the *whiB7* mutant, suggesting that *whiB7* positively autoregulates its own transcription.

Multidrug Resistance in a Monocyte Model System. The physiology of *Mycobacterium* growing in laboratory cultures is much different from their natural state during host cell infection (36). To investigate whether *whiB7* controls survival or antibiotic resistance in a eukaryotic cellular environment, we monitored the intracellular survival of *M. bovis* bacillus Calmette-Guérin and a constructed isogenic *whiB7* mutant harbored within untreated or spectinomycin-treated J774, a monocyte-like cell line most commonly used for antibiotic sensitivity testing. In the absence of antibiotic, the wild type and *whiB7* mutant had similar survival curves in resting or IFN-γ-activated J774 during the first 72 h of infection (Fig. 4*a*). Compared to liquid cultures, both bacillus Calmette-Guérin wild type and the *whiB7* mutant were more sensitive to spectinomycin in J774. However, more importantly, in resting J774, the *whiB7* mutant was >10-fold more sensitive to spectinomycin (as reflected by the concentration of antibiotic needed to reduce transcription by 50%; Fig. 4*b*).

Discussion

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The fact that the *whiB7* gene and its multidrug resistance phenotype have been retained in most Actinomycetes, including those that have not been continuously exposed to antibiotics in the environment, provides important insights into the evolution and biological function of "antibiotic resistance" genes and their regulatory systems. There are 14 genes belonging to the *whiB* family in the sequenced genome of *S. coelicolor* (23). Site-directed mutagenesis of this set of genes (B. Gust and K. Chater, personal communication) has shown that, like *whiB7*, many do not have obvious sporulation (white) defects under standard growth conditions and that the multidrug sensitive phenotype is a unique characteristic of *whiB7* mutants (L.N. and C.J.T., unpublished results). Studies of *whiB* paralogs in *Mycobacterium* species have shown that the *M. smegmatis whiB2* gene (also called *whmD*) is essential (37) and that another, *whiB3*, plays a role in virulence in some model systems (25). Here we focus on the ability of *whiB7* to determine multiple antibiotic resistances in Actinomycetes and suggest that, in mycobacterial species, it acts synergistically with a rather impermeable cell envelope to provide high levels of intrinsic resistance.

whiB7 is notably different from systems reported in other bacteria that allow adaptation to a variety of different nonspecific stress conditions and may incidentally provide multiantibiotic resistance. *whiB7* does not confer resistance to antiseptics, but rather to antibiotics having specific targets (see Figs. 5 and 6). *whiB7* function is also unique in that it confers relatively high levels of resistance: in the *S. lividans* mutant, antibiotic sensitivity increased by orders of magnitude; this is distinct from the general stress adaptive system, which confers much lower levels of multidrug resistance (*mar*) in enteric bacteria (17, 38) by using any one of three transcriptional activators having highly redundant functions.

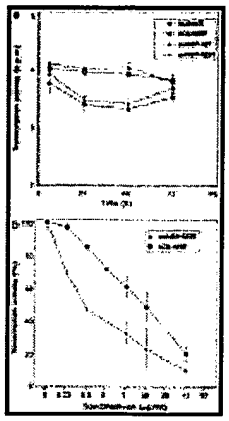

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Fig. 4. The phenotype of the *whiB7* mutation in J774, a monocyte-derived cell line. Mycobacterial RNA transcription, an indicator of survival, was assayed by incorporation of tritiated uracil. Shown are mean values (±SD) of six to eight determinations. Resting (REST) or activated (ACT) J774 monocytes growing in microtiter plates were exposed to *M. bovis* bacillus Calmette-Guérin and the corresponding *whiB7* mutant. (*a*) RNA synthesis of internalized WT and *whiB7* mutant cells decreased at the same rate in resting or activated monocytes, presumably because of bactericidal activity of the monocytes. In contrast, growth did occur in the control experiment where the bacteria were cultured in the same medium without monocytes (data not shown). (*b*) For antibiotic susceptibility testing, infected monocytes were incubated with medium containing the indicated concentrations of spectinomycin; % transcriptional activity is the percentage of incorporation rates in spectinomycin-treated vs. untreated bacteria. The same results were obtained in infected monocytes treated with amikacin after infection to confirm that incorporation rates reflected internalized mycobacteria (data not shown).

whiB7 is a putative transcriptional activator that is induced by antibiotics and controls the expression of at least two documented antibiotic resistance genes. The presence of these structural genes and corresponding regulatory systems in *Mycobacterium* suggests that this system provides selective advantage. The retention of the multiple antibiotic-responsive regulatory system controlling *M. tuberculosis whiB7* provides circumstantial evidence that toxic metabolites of various structures may have played a key role in directing the early evolution of the regulon to provide antibiotic resistance. The *whiB7* gene, as well as 5 of its 10 *M. tuberculosis* target genes (Fig. 3*a*), are present in *M. leprae* (Rv1473, Rv1257c, Rv1258c, Rv0263, and Rv2725), whose genome has undergone dramatic reduction during evolution within metazoan (presumably mammalian) hosts. The presence of the functionally conserved *whiB7* locus in all *Streptomyces* and *Mycobacterium* spp. (also including saprophytic *M.*

smegmatis) genomes now sequenced records its origin in their presumed soil dwelling ancestor. Although it is not clear why this capacity should be retained by *M. tuberculosis* and *M. leprae*, long after their progenitor left the antibiotic containing soil, some of these genes may have been adapted to protect the microbe against compounds of the mammalian immune system. The *whiB7* system was active in a monocyte model system; mutant was more sensitive to spectinomycin in J774 (Fig. 4*b*).

This evolutionary retention of *whiB7*, along with the observation that antibiotics with different structures activate it, implies a common endogenous inducer made by actinomycetes in response to antibiotics. Indeed, sublethal concentrations of some antibiotics induce synthesis of other secondary metabolites as demonstrated in *Streptomyces* (Figs. 1*B* and 5) that may also be autotoxic. Although *Mycobacterium* species are not recognized as antibiotic producers, they do have a remarkably large repertoire of polyketide biosynthesis gene clusters (39), some of which may encode biosynthetic pathways for autotoxic compounds.

Fatty acids, serving as precursors for diverse lipids and for the assembly of biological membranes, are nevertheless toxic to a wide variety of bacteria. Unlike most other bacteria, and for reasons that are not well understood, Actinomycetes commonly synthesize and accumulate extremely large amounts (20-80% of their biomass) of triacyl glycerols (40). This includes the primary precursor of complex lipids, palmitic acid, along with several unsaturated fatty acid derivatives, oleic, linoleic (unpublished data) and arachidonic (unpublished data) acids. All induced *whiB7*, with palmitic acid being the most active (Fig. 3*e*). The fact that the *whiB7* regulon, including antibiotic resistance genes, can be activated by palmitic acid has important implications for mycobacterial chemotherapy. Palmitic acid has been found in mycobacterial cytosol, and is considered to be a major source of carbon used by *M. tuberculosis* in the mammalian macrophage (41). It is also the principle fatty acid found in animal tissues

and serum. Therefore, the *whiB7* regulon may be induced when *M. tuberculosis* enters macrophages or other lipid rich cells, organs, or tissues, thereby allowing mycobacteria to more effectively resist some chemotherapeutic strategies, sheltered in specific areas of the body.

The intrinsic resistance of *M. tuberculosis* to antibiotics during *in vivo* growth and persistence underlies the need for protracted therapy for tuberculosis (2). Knowledge of such inducible intrinsic mycobacterial systems could generate derivatives of antibiotics that might circumvent detection by *whiB7* regulators or perhaps WhiB7 inhibitors that augment conventional therapies by inactivating groups of genes that confer intrinsic resistance. Such developments could not only open up a powerful repertoire of currently redundant clinical antibiotics in the treatment of tuberculosis but also reduce the problematic duration of chemotherapy.

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Footnotes

Author contributions: R.P.M., L.N., G.S., and C.J.T. designed research; R.P.M., L.N., J.G., K.N., D.S., S.E., and Y.L. performed research; R.P.M., L.N., J.G., K.V., L.H., J.P., G.S., and C.J.T. contributed new reagents/analytic tools; R.P.M., L.N., J.G., K.V., J.P., G.S., and C.J.T. analyzed data; and R.P.M., L.N., G.S., and C.J.T. wrote the paper.

Freely available online through the PNAS open access option.

Data deposition: The sequence reported in this paper has been deposited in the GenBank database (accession no. AF205848 [GenBank]).

§ Present address: Cubist Pharmaceuticals, 65 Hayden Avenue, Lexington, MA 02421.

** To whom correspondence should be addressed. E-mail: charles.thompson@ubc.ca .

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ATTACHMENT 5

CUSTOMER NO. 36257

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Virginia Goss TUSHER et al.		
Title:	Significance Analysis of Microarrays		
Application No.:	09/811,762	Filing Date:	March 19, 2001
Examiner:	Lori A. CLOW	Group Art Unit:	1631
Docket No.:	STAN.058US1	Conf. No.:	8102

Mail Stop Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GILBERT CHU IN SUPPORT OF AMENDMENT TO OVERCOME 35 U.S.C. § 101 REJECTION

Sir/Madam:

I, Dr. Gilbert Chu, hereby declare as follows:

1. I am one of the inventors of the above-identified application,

2. SAM software that is referred to in the attached Bulletin "SAM: Significance Analysis Microarrays: Supervised learning software for genomic expression data mining" has been widely licensed to the public since 2001.

3. Two other co-authors and I published the article "*Significance analysis of microarrays applied to the ionizing radiation response*," Virginia Goss Tusher, et al., Proceedings of the National Academy of Sciences of the United States of America (PNAS), which was published April 24, 2001, Volume 98, No. 9, pages 5116-5121. This article is referred to herein as the "SAM article."

4. Attached is an article entitled "An expression signature for p53 status in human breast cancer predicts mutation status, transcriptional effects, and patient survival," by Lance Miller et al., published in PNAS, September 20, 2005, Volume 102, No. 38, pages 13550-13555. As stated on page 6 of this article: "Univariate analysis by statistical analysis of microarrays (SAM) (22) identified 6,545 Affymetrix probe sets representing ≈ 5,290 distinct genes whose expression patterns distinguished P53 mt and wt tumors with a false discovery rate (q value) < 1% and d score (modified t statistic) > 2.0 ..., further illuminating the extensive nature of the molecular variation underlying p53 status." Reference to "statistical analysis of microarrays (SAM) (22)" in the Miller article refers to the SAM article.

5. Attached is an article entitled "Ancestral antibiotic resistance in Mycobacterium tuberculosis," by Rowan P. Morris, et al., published in PNAS, August 23, 2005, Volume 102, No. 34, pages 12200-12205. As described on page 5 of this article by Morris et al., monocytes were infected by mycobacterium and activated. Labeling of RNA and hybridizations were performed. Then, "data from each experimental condition was analyzed separately by using significance analysis of microarrays (22) with a false discovery ratio ≤ 0.3%." The reference to "significance analysis of microarrays (22)" is to the SAM article.

6. All of the independent Claims of the above-identified application include the limitation that an expected value of the parameter is derived and compared to an observed or calculated value of the parameter, where the expected value is indicative of the extent of variations in the parameter introduced by the process by which the data (called associated values in the claims) are acquired. Claims 1, 44 and 58 also contain the limitation that the parameters of the plurality of genes be adjusted so that variables related to the parameters are substantially independent of variations of scatter values or average associated values of the genes over the sets, said scatter values defined by standard deviation of the associated values in the sets.

7. I believe that the analyses using SAM in the above quotes from the Miller and Morris articles employ the two claim limitations of paragraph 6 above through the use of SAM software.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Dated: 7/20/06

Gilbert Chu